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Alcohol Consumption and All-Cause Mortality: A Systematic Review

2020 Dietary Guidelines Advisory Committee,
Beverages and Added Sugars Subcommittee

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Nutrition Evidence Systematic Review
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This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee in collaboration with the Nutrition Evidence Systematic Review (NESR) team at the Center for Nutrition Policy and Promotion, Food and Nutrition Service, U.S. Department of Agriculture (USDA). All systematic reviews from the 2020 Advisory Committee Project are available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews.

Conclusion statements drawn as part of this systematic review describe the state of science related to the specific question examined. Conclusion statements do not draw implications, and should not be interpreted as dietary guidance. This portfolio provides the complete documentation for this systematic review. A summary of this review is included in the 2020 Advisory Committee's Scientific Report available at www.DietaryGuidelines.gov.

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USDA and HHS implemented a process to identify topics and scientific questions to be examined by the 2020 Dietary Guidelines Advisory Committee. The Committee conducted its review of evidence in subcommittees for discussion by the full Committee during its public meetings. The role of the Committee members involved establishing all aspects of the protocol, which presented the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria;

[i] Under contract with the Food and Nutrition Service, United States Department of Agriculture.

reviewing all studies that met the criteria they set; deliberating on the body of evidence for each question; and writing and grading the conclusion statements to be included in the scientific report the 2020 Committee submitted to USDA and HHS. The NESR team with assistance from Federal Liaisons and Project Leadership, supported the Committee by facilitating, executing, and documenting the work necessary to ensure the reviews were completed in accordance with NESR methodology. More information about the 2020 Dietary Guidelines Advisory Committee, including the process used to identify topics and questions, can be found at www.DietaryGuidelines.gov. More information about NESR can be found at NESR.usda.gov.

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INTRODUCTION

This document describes a systematic review conducted to answer the following question: What is the relationship between alcohol consumption and all-cause mortality? This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee, supported by USDA's Nutrition Evidence Systematic Review (NESR).

More information about the 2020 Dietary Guidelines Advisory Committee is available at the following website: www.DietaryGuidelines.gov.

NESR specializes in conducting food- and nutrition-related systematic reviews using a rigorous, protocol-driven methodology. More information about NESR is available at the following website: NESR.usda.gov.

NESR's systematic review methodology involves developing a protocol, searching for and selecting studies, extracting data from and assessing the risk of bias of each included study, synthesizing the evidence, developing conclusion statements, grading the evidence underlying the conclusion statements, and recommending future research. A detailed description of the systematic reviews conducted for the 2020 Dietary Guidelines Advisory Committee, including information about methodology, is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews. In addition, starting on page 85, this document describes the final protocol as it was applied in the systematic review. A description of and rationale for modifications made to the protocol are described in the 2020 Dietary Guidelines Advisory Committee Report, Part D: Chapter 11. Alcoholic Beverages.

List of abbreviations

Abbreviation	Full name
ACM	All-cause mortality
CNPP	Center for Nutrition Policy and Promotion
CVD	Cardiovascular disease
DPS	Division of Prevention Science
FNS	Food and Nutrition Service
HDI	Human development index
HHS	United States Department of Health and Human Services
NESR	Nutrition Evidence Systematic Review
OASH	Office of the Assistant Secretary for Health
ODPHP	Office of Disease Prevention and Health Promotion
ONGA	Office of Nutrition Guidance and Analysis
PCS	Prospective cohort study
RCT	Randomized controlled trial
UK	United Kingdom
USDA	United States Department of Agriculture

WHAT IS THE RELATIONSHIP BETWEEN ALCOHOL CONSUMPTION AND ALL-CAUSE MORTALITY?

PLAIN LANGUAGE SUMMARY

What is the question?

- The question is: What is the relationship between alcohol consumption and all-cause mortality?

What is the answer to the question?

- **Primary comparisons (among those who currently drink alcohol)**
    - Moderate evidence indicates that higher average alcohol consumption is associated with an increased risk of all-cause mortality compared with lower average alcohol consumption among those who drink.
    - Moderate evidence indicates that binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) is associated with increased risk of all-cause mortality, and that more frequent binge drinking is associated with increased risk of all-cause mortality compared with less frequent or no binge drinking among those who drink.
- **Secondary comparison (between those who currently drink alcohol and those who have never consumed alcohol)**
    - Limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol. However, in light of the many scientific and public health issues associated with alcoholic beverages, any conclusions about low average consumption compared to never drinking alcohol require careful consideration.

Why was this question asked?

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.

How was this question answered?

- The 2020 Dietary Guidelines Advisory Committee, Beverages and Added Sugars Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.

What is the population of interest?

- The evidence includes alcohol consumption and all-cause mortality in primarily adults ages 21 years and older.

What evidence was found?

- This review includes 60 articles.
- The review is divided into 2 parts: evidence that compares people who drink

different amounts of alcohol, and evidence that compares people who drink alcohol with people who never drank alcohol.

- All-cause mortality is the number of deaths from all causes (rather than from specific causes like cardiovascular disease or cancer) during a specific time period.
- For the primary comparisons among those who currently drink alcohol:
    - Higher compared to lower average volume of alcohol consumption was related to higher all-cause mortality.
    - More frequent compared with less frequent or no binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) was related to higher all-cause mortality.
- For the secondary comparison between those who currently drink alcohol and those who have never consumed alcohol:
    - About half of the studies reported significant findings that low average alcohol consumption (particularly without binge drinking) compared with never drinking alcohol was associated with lower risk of mortality.
    - About half of the studies indicated no significant relationship.
    - Studies had several limitations. Factors other than drinking alcohol may impact all-cause mortality, and these factors were not always carefully addressed by the studies. The studies tended to examine middle- and older-aged adults, only. Some studies only measured alcohol consumption once, and that one measurement may not reflect participants' usual consumption. Studies varied in how they defined a "low-average" volume of alcohol.

How up-to-date is this systematic review?

- This review searched for studies from January 2010 to March 2020.

TECHNICAL ABSTRACT

Background

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.
- The 2020 Dietary Guidelines Advisory Committee, Beverages and Added Sugars Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.
- The goal of this systematic review was to examine the following question: What is the relationship between alcohol consumption and all-cause mortality?

Conclusion statements and grades

- **Primary comparisons (among those who currently drink alcohol)**
    - Moderate evidence indicates that higher average alcohol consumption is associated with an increased risk of all-cause mortality compared with lower average alcohol consumption among those who drink. (Grade: Moderate)
    - Moderate evidence indicates that binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) is associated with increased risk of all-cause mortality, and that more frequent binge drinking is associated with increased risk of all-cause mortality compared with less frequent or no binge drinking among those who drink. (Grade: Moderate)
- **Secondary comparison (between those who currently drink alcohol and those who have never consumed alcohol)**
    - Limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol. However, in light of the many scientific and public health issues associated with alcoholic beverages, any conclusions about low average consumption compared to never drinking alcohol require careful consideration. (Grade: Limited)

Methods

- A literature search was conducted using 3 databases (PubMed, Cochrane, and Embase) to identify articles that evaluated the intervention or exposure of alcohol consumption and the outcome of all-cause mortality. A manual search was conducted to identify articles that may not have been included in the electronic databases searched. Articles were screened by two NESR analysts independently for inclusion based on pre-determined criteria.
- Data extraction and risk of bias assessment were conducted for each included study, and both were checked for accuracy. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement(s), and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability.

Summary of the evidence

- Sixty studies that met the inclusion criteria for this systematic review addressing alcohol consumption and all-cause mortality were identified through the literature search from January 2010 to March 2020.
    - The body of evidence included one Mendelian randomization study, one retrospective cohort study, and 58 prospective cohort studies. The evidence included no RCTs.
- Consistent evidence reported increased all-cause mortality among those with higher average volume of alcohol consumption compared to lower average alcohol consumption. Although consumption categories varied, among those who drank alcohol most studies found lower risk among men consuming within ranges up to 2 drinks per day and women consuming within ranges up to 1 drink per day compared to those consuming higher average amounts. Among studies assessing continuous distributions or based on dose-response relationships among narrower consumption ranges among men who drink, the lowest levels of risk were generally up to 1 or 1.5 drinks on average (depending on how consumption was categorized). Relatively few studies among women examined risk based on categories within the range of up to 1 drink per day on average.
- Consistent evidence among those who drink alcohol reported higher all-cause mortality with more frequent binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) compared with less frequent or no binge drinking.
- For the secondary comparison between current drinkers and never drinkers, the limited available evidence suggested that low average consumption was associated with lower risk of mortality compared with never drinking status. Included studies were a subset of the 60 studies above that were used to assess the primary comparisons of interest.
- Twenty-five studies compared those who consumed alcohol with never drinkers. Approximately half of the studies reported significant findings that low average alcohol consumption (particularly without binge drinking) was associated with reduced risk of all-cause mortality compared with never drinking alcohol, approximately half of the studies indicated no significant relationship, and two studies reported that low alcohol consumption was significantly associated with greater all-cause mortality compared to never drinking alcohol.
- Generally, the evidence was limited by inadequate adjustment for confounders, selection bias and limited generalizability (studies often included only middle- and older-aged adults), and potential misclassification or bias from an exposure assessment based on single-time measurements of alcohol consumption. Low average volume was classified variably.
- Because the studies provided no consistent definition or categorization of higher average or lower average consumption, these terms are used in a descriptive sense in the conclusion statement. However, across most studies definitions of binge drinking or levels that corresponded to binge drinking were generally consistent; thus binge drinking is defined based on a set number of drinks in the conclusion statement.

FULL REVIEW

Systematic review question

What is the relationship between alcohol consumption and all-cause mortality?

Conclusion statements and grades

Primary comparisons (among those who currently drink alcohol)

Moderate evidence indicates that higher average alcohol consumption is associated with an increased risk of all-cause mortality compared with lower average alcohol consumption among those who drink. (Grade: Moderate)

Moderate evidence indicates that binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) is associated with increased risk of all-cause mortality, and that more frequent binge drinking is associated with increased risk of all-cause mortality compared with less frequent or no binge drinking among those who drink. (Grade: Moderate)

Secondary comparison (between those who currently drink alcohol and those who have never consumed alcohol)

Limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol. However, in light of the many scientific and public health issues associated with alcoholic beverages, any conclusions about low average consumption compared to never drinking alcohol require careful consideration. (Grade: Limited)

Summary of the evidence

- Sixty studies that met the inclusion criteria for this systematic review addressing alcohol consumption and all-cause mortality were identified through the literature search from January 2010 to March 2020.[1-60]
    - The body of evidence included one Mendelian randomization study, one retrospective cohort study, and 58 prospective cohort studies. The evidence included no RCTs.
- Consistent evidence reported increased all-cause mortality among those with higher average volume of alcohol consumption compared to lower average alcohol consumption. Although consumption categories varied, among those who drank alcohol most studies found lower risk among men consuming within ranges up to 2 drinks per day and women consuming within ranges up to 1 drink per day compared to those consuming higher average amounts. Among studies assessing continuous distributions or based on dose-response relationships among narrower consumption ranges among men who drink, the lowest levels of risk were generally up to 1 or 1.5 drinks on average (depending on how consumption was categorized). Relatively few studies among women examined risk based on categories within the range of up to 1 drink per day on average.

- Consistent evidence among those who drink alcohol reported higher all-cause mortality with more frequent binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) compared with less frequent or no binge drinking.
- For the secondary comparison between current drinkers and never drinkers, the limited available evidence suggested that low average consumption was associated with lower risk of mortality compared with never drinking status. Included studies were a subset of the 60 studies above that were used to assess the primary comparisons of interest.
- Twenty-five studies compared those who consumed alcohol with never drinkers. Approximately half of the studies reported significant findings that low average alcohol consumption (particularly without binge drinking) was associated with reduced risk of all-cause mortality compared with never drinking alcohol, approximately half of the studies indicated no significant relationship, and two studies reported that low alcohol consumption was significantly associated with greater all-cause mortality compared to never drinking alcohol.
- Generally, the evidence was limited by inadequate adjustment for confounders, selection bias and limited generalizability (studies often included only middle- and older-aged adults), and potential misclassification or bias from an exposure assessment based on single-time measurements of alcohol consumption. Low average volume was classified variably.
- Because the studies provided no consistent definition or categorization of higher average or lower average consumption, these terms are used in a descriptive sense in the conclusion statement. However, across most studies definitions of binge drinking or levels that corresponded to binge drinking were generally consistent; thus binge drinking is defined based on a set number of drinks in the conclusion statement.

Description of the evidence

Primary and secondary comparisons

This systematic review examined available evidence on the relationship between alcohol consumption and all-cause mortality in adults ages 21 years and older. Studies that exclusively enrolled participants younger than age 21 years were excluded to focus on the primary population of interest.

The search range included peer-reviewed articles published from January 2000 to March 2020. However, due to time constraints, the Committee revised their protocol to focus the review on studies published from January 2010 to March 2020. Studies were included if they were conducted in countries categorized as high or very high on the Human Development Index[ii]. Study designs that were included were: RCTs, non-

[ii] The Human Development classification was based on the Human Development Index (HDI) ranking (1) from the year the study intervention occurred or data was collected. If the study did not report the year in which the

randomized controlled trials, prospective and retrospective cohort studies, nested case-control studies, and Mendelian randomization studies. Studies were included if the study participants were generally healthy or at risk for chronic disease and for cohort studies that had sample sizes greater than 1,000 enrolled participants. Relationships between differing average alcohol consumption or patterns among those who drink was examined as a primary comparison. Although the primary comparison was different levels of alcohol consumption among those who currently drink, relationships between those who currently drink and those who have never consumed alcohol (i.e., lifetime abstainers) were also examined as a secondary comparison. Of note, articles were excluded if the reference group were "non-drinkers" who comprised those who used to drink but no longer drink ("former drinkers") or a combination of lifetime abstainers and former drinkers. In papers that met all inclusion criteria, if the analysis included a non-reference group that combined never drinkers and former drinkers, these data were not extracted and therefore not used during synthesis.

The body of evidence included 60 articles (see **Table 1**): one Mendelian randomization study,[1] one retrospective cohort study,[16] and 58 prospective cohort studies.[2-15,17-60] The evidence included no RCTs.

Population

The Mendelian randomization study enrolled male participants of Caucasian origin who were 65 to 84 years old.[1] The study was conducted in Australia and the analytic sample size was 3496.

Among the cohort studies, many studies examined adults of middle age and older (i.e., ages 45 and older); however, some population-based studies of adults (e.g., ages 18 years and older) or more representative age groups (e.g., ages 35 to 75 years) were included for both average consumption and patterns of consumption. Analytic sample sizes ranged from 1,121 to 599,912 participants; the majority (76%) of studies had analytic sample sizes greater than 10,000 participants. The majority (53%) of the prospective studies were from Europe (Belarus, Denmark, France, Germany, Greece, Hungary, Italy, Lithuania, The Netherlands, Norway, Poland, Russia, Spain, Sweden, and the United Kingdom). Several studies (36%) were from the United States. Several other high or very high HDI countries were represented, including: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Korea, Singapore, and Turkey. Four studies were conducted in all-male samples,[5,30,40,47] and four studies were in all-female samples.[27,33,44,48]

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intervention occurred or data was collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank (2) is used instead; 1. UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data; 2. The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world- country-and-lending-groups

Intervention/exposure/comparator

The interventions or exposures of interested were average consumption of alcoholic beverages and the pattern of consumption of alcoholic beverages (i.e., the number of drinks per drinking day or drinks per drinking occasion, such as binge drinking). Information on the type of beverage (e.g., beer, wine, spirits) was collected if available. The primary comparator of interest was differing average alcohol consumption or patterns among those who currently drink. The secondary comparison was between those who currently drink and those who have never consumed alcohol (i.e., lifetime abstainers). Studies were excluded if the reference group were "non-drinkers" that comprised of former drinkers or a combination of never and former drinkers.

The Mendelian randomization study examined average alcohol consumption as drinks per day on an average week and compared never drinkers, past drinkers, and different levels of daily consumption among those who currently drink.[1] Alcohol consumption was measured once at baseline, and the study did not control for pattern of alcohol consumption.

Among the 59 cohort studies, 40 studies examined average alcohol consumption only, two studies measured alcohol consumption patterns only, and 16 studies measured both but often in quantity-frequency combinations that made it difficult to disaggregate effects of quantity consumed per drinking day from effects of frequency. There were 25 studies that addressed the relationship between those who currently drink and never drinkers; one study did not provide data on the average amount consumed or drinking pattern among those who currently drink.[40] The majority of studies were based on categorical alcohol consumption (e.g., lifetime abstainer, light, moderate, and heavy drinkers); seven studies reported continuous consumption measures among those who currently drink.[2,7,13,35,38,46,56] Most studies (63%) did not control for average alcohol consumption or pattern of consumption in the analysis for pattern of consumption and average consumption, respectively. Furthermore, most studies (86%) assessed alcohol consumption only at one point in time (baseline). Three studies reported results on the type of alcoholic beverage (such as beer, cider, champagne, wine, liquor and spirits) in addition to overall alcohol consumption,[10,35,56] and one study reported results only by type of alcoholic beverage.[46]

Outcome

The endpoint outcome for this systematic review was all-cause mortality (i.e., total mortality), which was defined as the total number of deaths from all causes during a specific time period. Although some studies disaggregated causes of death, the outcome for this review did not include cause-specific mortality (i.e., total number of deaths from a specific disease, such as CVD or cancer).

There were 35 studies that reported all-cause mortality among men and women combined[6-16,21,25,26,28,31,34-39,45,46,50-60]; 26 studies provided results stratified by sex,[2-4,9,11-13,15-18,20,22-24,28,29,32,34,41-43,49,56,58,59] four studies were in all-male samples,[5,30,40,47] and four studies were in all-female samples.[27,33,44,48] Most studies directly measured all-cause or total mortality as the outcome; however, two studies measured all-cause mortality indirectly. Bellavia et al[2] measured differences in 10th survival percentile (point in time by which the first 10% of the cohort has died), and van den Brandt et al[56] measured the risk of reaching longevity until age 90.

Evidence synthesis

Primary comparisons (among those who currently drink alcohol)

The majority of studies examining the relationship between alcohol consumption and all-cause mortality found a statistically significant relationship (**Table 1**).

The Mendelian randomization study reported that among older men (70 to 89 years), having a genetic variant associated with reduced alcohol consumption was associated with lower total mortality.[1] However, the study did not distinguish between various levels of consumption by genetic variant.

Among the 59 cohort studies, over half reported a significant association between higher average volume of consumption and higher all-cause mortality compared to lower average volume consumption, with generally consistent dose-response relationships, at least with respect to point estimates. Among those who drink, most studies found lower risk among men consuming between 0 and 2 drinks per day, and women consuming between 0 and 1 drink per day. Among studies assessing continuous distributions or based on dose-response analyses among narrower average consumption ranges, approximately half of the studies found lower risks for men consuming at or below approximately 1 to 1.5 drinks per day compared to those consuming higher average amounts. Few studies among women examined categories of risk within the 0 to 1 range of average drinks.

In the body of evidence, 18 observational studies examined drinking patterns. Three studies assessed the relationship between the usual number of drinks typically consumed per drinking day or occasion and all-cause mortality. Among men, 3 studies found that consuming more than 2 drinks per drinking day was associated with higher mortality risk compared with consuming less; only 1 study examined differences among men comparing 1 vs 2 drinks. For women, both studies found increased risk for all-cause mortality with consumption greater than 1 drink. The majority of studies examining drinking patterns assessed relationships based on binge drinking (typically defined as consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion). Although not all studies defined binge drinking in the same manner, studies consistently found that among those who drink, binge drinking was associated with increased mortality risk compared to not binge drinking, and that more frequent binge drinking was associated with increased risk compared with less frequent binge drinking.

Funding sources were documented during data extraction for consideration when reviewing this evidence. Further, publication bias is always a consideration in systematic reviews.

Assessment of the evidence[iii]

1. Average consumption among those who currently drink alcohol:

The following conclusion statement was assigned a grade of moderate: "Moderate evidence indicates that higher average alcohol consumption is associated with an increased risk of all-cause mortality compared with lower average alcohol consumption among those who drink."

As outlined and described below, the body of evidence examining average consumption among those who currently drink alcohol and all-cause mortality was assessed for the following elements when grading the strength of evidence.

Consistency: A relatively large number of studies informed the primary comparisons, with generally consistent findings for both the United States and other high-income nations on the association between average alcohol consumption and all-cause mortality. However, studies used different levels of comparison (and terminology) to define lower versus higher average consumption. Further, for lower average consumption, some studies assessed a subgroup of those who consumed very small amounts of alcohol and/or had infrequent consumption. Although their risk was generally less than for higher average consumption, findings were inconsistent about whether they had higher risk than lower average volume drinkers. Not all studies reported consumption in grams of ethanol, but rather in drinks per day or per week.

Directness: The studies were designed to directly examine the relationships among alcohol consumption, the comparator, and all-cause mortality in the systematic review question. All studies assessed alcohol consumption, and most examined average consumption only with a few that accounted for volume and pattern concurrently.

Precision: The Mendelian randomization study had a relatively small size (<4000 participants), particularly for this type of study. However, there were numerous observational studies with relatively large sample sizes. Exposures were often categorical, and rarely continuous. Studies using "occasional or light" drinkers as the reference group had less precision to the extent that occasional drinkers are not a large proportion of most study populations; this makes it difficult to interpret overlapping confidence intervals between "moderate" and heavier drinkers since direct comparisons between those groups should yield narrower confidence intervals.

Generalizability: Since most studies were in older age cohorts, selection bias based on the age of the study cohorts is a possibility. A large percentage of alcohol-attributable deaths occur before age 50 years, and those who have been established moderate drinkers for longer periods or until later in life may be advantaged, socially, or in terms of health. Studies of older cohorts could lead to underestimation of alcohol-mortality associations compared with studies that are population-based.

[iii] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

Risk of bias: There were a number of potential risks of bias, or limitations across the body of evidence (see summary of risk of bias in **Table 2**). The evidence included no RCTs. Assessed studies did not control for multiple key confounders (e.g., socioeconomic factors, diet quality), and did not typically account for patterns of alcohol consumption. Failing to account for patterning as a confounder may affect the generalizability of studies because people participating in surveys or cohorts may have different patterns of consumption (i.e., less binge drinking) or alcohol-related problems compared to people in the general population, even among those with similar consumption levels. Selection bias is also a concern, mostly due to the age of participants as noted above, and measurement of exposure because it is almost always self-report. Furthermore, the majority of studies measured alcohol at one point in time contributing to risk of bias from deviations from the assessed exposure resulting in possible misclassification of typical average consumption. Measuring consumption at one point in time also precludes assessments related to drinking trajectories over time, or the effects of cumulative alcohol consumption over the life course. Alcohol consumption typically changes throughout the life course.

2. Binge drinking among those who drink:

The following conclusion statement was assigned a grade of moderate: “Moderate evidence indicates that binge drinking (consuming 5 or more drinks for men or 4 or more drinks for women during a drinking occasion) is associated with increased risk of all-cause mortality, and that more frequent binge drinking is associated with increased risk of all-cause mortality compared with less frequent or no binge drinking among those who drink.”

As outlined and described below, the body of evidence examining binge drinking among those who drink alcohol and all-cause mortality was assessed for the following elements when grading the strength of evidence.

Consistency: Findings were generally consistent in terms of the direction of association, magnitude and significance even though not all studies defined binge drinking the same way.

Directness: Studies were designed to directly examine the relationships among the alcohol pattern, comparator, and all-cause mortality in the systematic review question. However, not all studies measured alcohol pattern in the same manner and few accounted for volume and pattern concurrently.

Precision: The observational studies had relatively large sample sizes. However, exposures were often categorical, and therefore were less precise.

Generalizability: Studies may have included participants with less binge drinking or other risky patterns of consumption compared to studies of the general population, even among those with the same average consumption levels. This could lead to underestimates of alcohol-related risk in cohort or survey participants compared to the general population, and adversely affects the generalizability of findings. The majority of studies were conducted in European countries, and findings may not be generalizable to the United States. Confounders related to binge drinking may vary by gender, and few studies reported binge drinking in men and women separately.

Risk of bias: There were several potential risks of bias, or limitations across the body

of evidence (see summary of risk of bias in **Table 2**). There evidence included no RCTs. The risk of confounding bias was high overall. Assessed studies did not control for multiple key confounders (e.g., socioeconomic factors, diet quality), and did not typically account for average consumption. Despite the consistency and magnitude of findings, binge drinkers (or those consuming high average amounts) may have negative associated confounders. Selection bias is also a concern due to the age of participants, and measurement of exposure because it is almost always self-report. Furthermore, most studies measured alcohol at one point in time contributing to risk of bias from deviations from the assessed exposure resulting in possible misclassification of patterns of consumption compared to typical consumption over the life course.

Secondary comparison (between those who currently drink alcohol and those who have never consumed alcohol)

There were 25 studies that compared those who currently drink alcohol and those who have never consumed alcohol (**Table 1**). Approximately half of the studies reported significant findings that low average alcohol consumption (particularly without binge drinking) was associated with reduced risk of all-cause mortality compared with never drinkers. Approximately half of the data indicated no significant relationship between low average alcohol consumption and never consuming alcohol on all-cause mortality. Two studies reported that low alcohol consumption was significantly associated with greater all-cause mortality compared to never drinkers.[16,37] Horvat et al[16] found that participants from Russia, but not Belarus or Hungary, who drank up to once a month had significantly higher risk of all-cause mortality compared to never drinkers. A study from the United Kingdom reported that occasional drinkers (those who declared not having drunk in the past 7 days) had reduced risk of all-cause mortality compared to never drinkers, but those who consumed alcohol within the UK guidelines (<14 units per week for women; <21 units per week for men) or more had a greater risk of all-cause mortality compared to never drinkers.[37] Three studies reported that “high” average drinkers had greater risk of all-cause mortality compared to never drinkers.[17,35,51]

There are particularities worth nothing within this body of evidence, mainly regarding the population of those who never consumed alcohol (i.e., never drinkers). Definitions of never drinkers varied among studies. Furthermore, never drinkers may have more adverse confounding factors compared with those who drink, and all studies lacked inclusion of key confounders. A sizable fraction of self-described never drinkers may be former drinkers and are therefore misclassified. In addition, there were fewer studies of never drinkers than those of within-drinker comparisons; some studies were restricted to those who drink, while others assessed non-drinkers as a group and could not or did not disaggregate former drinkers from never drinkers.

Funding sources were documented during data extraction for consideration when reviewing this evidence. Further, publication bias is always a consideration in systematic reviews.

Assessment of the evidence[iv]

3. Low average consumption vs never drinking alcohol:

The following conclusion statement was assigned a grade of limited: “Limited evidence suggests that low average alcohol consumption, particularly without binge drinking, is associated with a lower risk of all-cause mortality compared with never drinking alcohol. However, in light of the many scientific and public health issues associated with alcoholic beverages, any conclusions about low average consumption compared to never drinking alcohol require careful consideration.”

As outlined and described below, the body of evidence examining low average alcohol consumption vs never drinking alcohol and all-cause mortality was assessed for the following elements when grading the strength of evidence.

Consistency: The data was largely either significant indicating lower all-cause mortality risk for low average alcohol consumption compared to never drinking alcohol, or non-significant. Few studies reported significant findings in the opposite direction.

Directness: While the review methods focused only on data from “never drinkers” rather than “non-drinkers” (which combines never and former drinkers), studies varied in their assignment and definition of never drinkers. Further, in some studies, due to self-report, participants may have incorrectly classified themselves as “never drinkers”.

Precision: Since “never drinkers” were a relatively small proportion of the study populations, confidence intervals tended to be wide, thus limiting precision.

Generalizability: This evidence cannot be generalized to inform never drinkers who are considering drinking alcohol; nor can it be generalized to inform those who currently drink to become “never drinkers”. Many study populations were not representative of the age distribution of all adults who typically begin to consume alcohol.

Risk of bias: There were a number of potential risks of bias, or limitations across the body of evidence (see summary of risk of bias in **Table 2**). There evidence included no RCTs. Risk of bias is a concern for this body of evidence, particularly related to additional confounding issues with the “never drinker” population. All studies lacked inclusion of key pre-specified confounders. There are also concerns around selection bias due to the age of participants at the time of data assessment and measurement of exposure because it is almost always self-report. Furthermore, the majority of studies measured alcohol at one point in time contributing to risk of bias from deviations from the assessed exposure resulting in possible misclassification of alcohol consumption.

[iv] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

Research recommendations

To better assess the relationship between alcohol consumption and all-cause mortality, future research may:

- Measure alcoholic beverage intake and consumption patterns with greater accuracy and determine their effect on human health through all appropriate life stages using more consistent and improved definitions, controls, and research methods, such as:
    - Stronger research designs, including randomized clinical trials, Mendelian randomization studies, and non-randomized intervention studies
    - Multiple measures of intake over time rather than at one time point
    - Distinction between lifelong never drinkers and either very low-level consumers or former drinkers who refer to themselves as never drinkers
    - Long timeframes for studies and better control for key confounders, including: sex, age, race/ethnicity, socioeconomic status, eating pattern or diet quality, physical activity, and smoking
    - Enrollment of younger and lower exposure drinkers who may have more adverse drinking outcomes
    - More research on patterns of consumption, including health outcomes in relation to the frequency and usual amount of alcohol consumed during drinking days
- Study the effects of alcohol consumption on:
    - Dietary patterns and overall diet quality
    - Growth, size, body composition, and risk of overweight and obesity
    - Risk of intermediate cardiovascular outcomes
    - Risk of type 2 diabetes, including markers for prediabetes
    - Risk of cancer, including mouth, throat, larynx, esophagus, colon and rectum, liver, and breast in women
    - Neurocognitive health, including alcohol consumption during lactation and neurocognitive health of the infant

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Table 1: Summary of articles that address the relationship between alcohol consumption and all-cause mortality[v]

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Almeida, 2017[1] Mendelian Randomization Study (PCS), Health in Men Study (HIMS) Australia N=3,496 **Participants:** ~77y (65-84y), 100% male; excluded: those with missing data on alcohol consumption or *ADH1B* rs1229984 G>A genotype, men of possible non-Caucasian origin	**Baseline:** 1996-1998 (for alcohol intake); 2001-2004 for DNA **Follow-up:** 2012, mean: 8y **Average intake: drinks/d on an average week** • ***Never drinker (REF)*** • Past: none in preceding year • ≤2 drinks/d • 2-4 drinks/d • 4-6 drinks/d • >6 drinks/d *ADH1B* rs1229984 G>A genotype assessed at first follow-up visit (2001-2004) (6.4% were carriers and consumed significantly less alcohol)	• Never drinker (REF) • Past: NS • ≤2 drinks/d: NS • 2-4 drinks/d: NS • 4-6 drinks/d: NS • **>6 drinks/d: 1.87 (1.11, 3.12)** **ACM HR by genotype** Carriers have lower mortality risk if alcohol is not consumed "We found evidence of a statistically significant interaction between alcohol use group and being a carrier."	**Key confounders:** Sex, age, race/ethnicity, SES (education), physical activity, smoking **Other factors considered:** anthropometry **Other:** prevalent coronary heart disease and stroke	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Older cohort: Potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • 6-year time lag between alcohol assessment and DNA assessment • No information on non-completers • No preregistered data analysis plan

[v] Abbreviations/short-hand: ACM: all-cause mortality; ADG: aggregated diagnosis group; adj: adjusted; AHEI: alternate healthy eating index; Avg: average; B: beta; BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; d: day(s); DGA: Dietary Guidelines for Americans; DM: diabetes mellitus; ECG: electrocardiogram; EER: estimated energy requirement; ETOH: ethyl alcohol; FFQ: food frequency questionnaire; g: gram(s); HEI: healthy eating index; HR: hazard ratio; HRT: hormone replacement therapy; IADL: instrumental activities of daily living; kg/m^2: kilograms per meters squared; ml: milliliters; mo: month(s); N/A: not applicable; NS: not significant; NR: not reported; occ: occasion; OR: odds ratio; PAR: population-attributable risks; PCS: prospective cohort study; PD: percentile difference; pts: points; RCT: randomized controlled trial; REF: reference group; RR: risk ratio; SD: standard deviation; SE: standard error; SES: socioeconomic status; UK: United Kingdom; unadj: unadjusted; wk: week(s); y: year(s)
Red font indicates a statistically significant detrimental relationship, and green font indicates a statistically significant beneficial relationship.

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Bellavia, 2014[2] Prospective Cohort Study, Cohort of Swedish Men and Swedish Mammography Cohort Sweden N=67,706 **Participants**: 45-83y (~60y), 46% female; excluded participants who reported incorrect or missing personal numbers, those who died before start of follow-up, those who had diabetes or any history of CVD and cancer, and those with missing information on all alcohol-related items; former drinkers were also excluded from the analysis	**Baseline**: 1997-1998 **Follow-up**: 2012 (15y) **Average intake: frequency (FFQ) + amount (per occasion)** • ***Lifetime abstainers (REF)*** • <1.5 g/d (women) • 1.5-5 g/d (women) or <5 g/d (men) • 5-10 g/d • 10-15 g/d • >15 g/d (women) or 15-20 g/d (men) • 20-25 g/d (men) • 25-30 g/d (men) • >30 g/d (men) 1 drink = 12g ETOH	**Differences in 10th survival percentile**, Laplace regression, 10th PD, months (95% CI) **Males:** • Lifetime abstainers (REF) • <5: NS • **5-10: 9 (-1, 18)** • **10-15: 16 (6, 25)** • **15-20: 14 (3, 24)** • 20-25: NS • 25-30: NS • >30: NS **Females:** • Lifetime abstainers (REF) • **<1.5: 15 (8, 23)** • **1.5-5: 17 (9, 24)** • **5-10: 22 (13, 30)** • **10-15: 13 (3, 23)** • **>15: 16 (5, 26)** **HR (95% CI)** **Males:** • Lifetime abstainers (REF) • <5: NS • **5-10: 0.86 (0.76, 0.97)** • **10-15: 0.77 (0.68, 0.88)** • **15-20: 0.80 (0.70, 0.93)** • 20-25: NS • 25-30: NS • >30: NS **Females:** • Lifetime abstainers (REF) • **<1.5: 0.81 (0.73, 0.89)** • **1.5-5: 0.77 (0.70, 0.85)** • **5-10: 0.72 (0.64, 0.81)** • **10-15: 0.74 (0.64, 0.85)** • **>15: 0.78 (0.68, 0.91)**	**Key confounders:** Sex, age, SES, physical activity, smoking **Other factors considered:** age distribution of the study sample, anthropometry, diabetes **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol pattern • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Bergmann, 2013[3] Prospective Cohort Study, European Prospective Investigation into Cancer and nutrition (EPIC) Denmark, France, Germany, Greece, Italy, Netherlands, Spain, and UK N=380,395 **Participants**: 25-70y (~52y), 71% female; excluded cohorts of France (female members of a health insurance for school employees), Utrecht (breast cancer screening attendees), Spain (mainly blood donors and their spouses), and Oxford (mainly vegetarian and health-conscious people), and study centers where information on alcohol use in the past was not collected; participants with no follow-up or information on vital status, those with missing data on dietary or lifestyle questionnaire or alcohol use in the past, and those whose ratio of energy intake to EER was in top or bottom 1%	**Baseline**: 1992-2000 **Follow-up**: 12.6y **Average intake: glasses/d by beverage type, converted to g/d—reflects past year avg and avg during each prior decade of life** • Never: no alcohol use at all points in time • Former light to moderate: ≤60 g/d (men) or ≤30 g/d (women) in the past but not at time of enrollment • Former heavy: >60 g/d (men) or >30 g/d (women) in the past but not at time of enrollment • ***Light (REF):*** ≤2 g/d (men) or ≤1 g/d (women) • Below rec. limits: ≤24 g/d (men) or ≤12 g/d (women) • Light to moderate: ≤60 g/d (men) or ≤30 g/d (women) • Occasionally heavy: >60 g/d (men) or >30 g/d (women) • Heavy: >60 g/d (men) or >30 g/d (women)	**Men** Never: NS **Former light to mod: 1.32 (1.11, 1.57)** **Former heavy: 2.00 (1.61, 2.50)** Light (REF) **Below rec. limits: 0.86 (0.74, 0.99)** Light to mod: NS Occasionally heavy: NS **Heavy: 1.57 (1.26, 1.96)** **Women** **Never: 1.16 (1.04, 1.30)** **Former light to mod: 1.23 (1.09, 1.39)** **Former heavy: 1.74 (1.22, 2.48)** Light (REF) **Below rec. limits: 0.91 (0.84, 0.99)** Light to mod: NS Occasionally heavy: NS Heavy: NS	**Key confounders:** Sex, age, SES (education), eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry, hypertension, diabetes **Other:** Center; self-reported cancer, myocardial infarction, or stroke; in women: menopausal status, menopausal hormone use, number of live births	• **Key confounders NOT accounted for**: race/ethnicity, alcohol intake • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Bobak, 2016[4] Prospective Cohort Study, Health, Alcohol and Psychosocial factors in Eastern Europe Russia, Lithuania, Poland N=34,304 **Participants**: 45-69y, 53% female, excluded those without linkage to death registry	**Baseline**: 2002-2005 **Follow-up**: 2010-2011 **Average daily alcohol intake for men/women:** • 0 g/d (combines never + former) • ***<10/5 g/d, REF*** • 10-60/5-20 g/d • >60/20 g/d **Drinking frequency:** • Never • ***<1/mo, REF*** • 1-3/mo • 1-4/wk • 5+/wk **Drinking pattern for men/women:** • ***Light drinker (REF):*** <2/0.5 drinks per occasion • Moderate drinker (<4/2 drinks per occasion) • Occasional heavy drinker (>4 drinks per occasion <1/wk) • Regular heavy drinker (>4 drinks per >1/wk) Binge drinking: >100/60 g of ethanol in one episode at least monthly ***(non-binge drinker, REF)***	Average daily alcohol intake for women (all NS in men): • <5 g/d, REF • 5-20 g/d: NS • **>20 g/d: 1.92 (1.25, 2.93)** Drinking frequency in men (similar in women): • <1/mo, REF • 1-3/mo: NS • 1-4/wk: NS • 5+/wk: NS Drinking pattern in men (similar in women): • Light drinker, REF • Moderate drinker: NS • Occasional heavy drinker: NS • Regular heavy drinker: NS Binge drinking in men (similar in women): • Non-binge drinker, REF • Binge-drinker: NS	**Key confounders:** Sex, age, SES (education, marital status, economic activity, asset score, subjective hardship score), eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry **Other:** Marital status, prevalent CVD or cancer, depressive symptoms, study center	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Older cohort: potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • Lowest level alcohol consumers likely included never and former drinkers • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Britton, 2010[5] Prospective Cohort Study, Whitehall II cohort study of British civil servants United Kingdom N= 5,411 **Participants**: 35-55y (~43y), 100% male; analysis restricted to those who were free of CHD at baseline and those who attended ≥3 phases to look at variability in alcohol intake; women were excluded since there were too few CHD events; men who reported on ≥3 separate occasions that alcohol frequency in last year was "none" were deemed "never drinkers" and excluded from analysis	**Baseline**: 1985-1988; Follow-up (exp data): Phase 2 (1989-90), Phase 3 (1991-94), Phase 5 (1997-99), and Phase 7 (2003-04); **Follow-up** (outcome): 2009 **Variability in average alcohol intake (SD of grouped alcohol levels)** • ***Low (REF):*** alcohol variability (SD≤0.5) • Medium alcohol variability (0.5<SD≤1.1) • High alcohol variability (SD>1.1) **Average alcohol consumption (baseline and average among drinkers)** • None • 1-7 units/wk • ***Moderate drinkers (REF):*** 8-14 units/wk • 15-21 units/wk • 22-28 units/wk • 29-35 units/wk • ≥36 units/wk	<u>Variability in intake</u> Low (REF) Medium: 1.00 (0.77, 1.29) **High: 1.52 (1.07, 2.17)** <u>Alcohol consumption</u> Figure only; Data NR	**Key confounders:** Sex, age, SES (civil service employment grade of low/med/high), smoking, average alcohol intake during follow-up **Other factors considered:** N/A **Other:** CHD	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity, alcohol pattern • Exposure data measurement tool not validated • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Britton, 2016[6] Prospective Cohort Study, Whitehall II cohort study of British civil servants United Kingdom N= 7,010 **Participants**: 47-67y, 29% female	**Baseline**: 1997-1999 **Follow-up**: 2015 (16-18y) **Average intake: reported for previous week by beverage type, converted to g/week** • Non-drinker • Former drinker: current non-drinker but indicated alcohol consumption in the past • ***Moderate (REF):*** within guidelines of 1–168 g (1–21 units) of ethanol per week for men and 1–112 g (1–14 units) for women) • Heavy: 169–407 g (22–50 units) for men and 113–287 (15–35 units) for women) • Very heavy: 408+g (51+ units) for men and 288+g (36+ units) for women Pre- and post-change conversion: before and after the legal introduction of standardized wine serving sizes in the UK and the shift from 125 to 175 ml glasses becoming the normative standard serving size; 1 glass of wine = 8g ETOH before 16g after	Pre-change conversion 1 glass of wine = 8g ETOH: • Non-drinker: 1.17 (0.91, 1.51) • Former drinker: 1.22 (0.97, 1.54) • Moderate: REF • Heavy: 1.05 (0.87, 1.26) • **Very heavy: 2.26 (1.67, 3.06)** Post-change conversion 1 glass of wine = 16g ETOH: • Non-drinker: 1.14 (0.88, 1.48) • Former drinker: 1.19 (0.94, 1.51) • Moderate: REF • Heavy: 0.90 (0.75, 1.08) • **Very heavy: 1.55 (1.23, 1.94)**	**Key confounders:** Sex, age, race/ethnicity, SES (civil service employment grade of low/med/high), eating pattern or diet quality, physical activity, smoking **Other factors considered:** N/A **Other:** N/A	• **Key confounders NOT accounted for**: alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Degerud, 2020[7] Prospective Cohort Study, The Age 40 Program; the Cohort of Norway (CONOR) Norway N= 243,372 **Participants**: ~44y, 52% female, mean BMI 25.7 kg/m^2; excluded participants with missing or inconsistent survey data on alcohol, mental health, or covariates	**Baseline**: 1994-2002 **Follow-up**: 2014 (~17y) **Average intake:** combined frequency & amount • Current abstainers: includes never and former drinkers (data not extracted) • ***Low (REF):*** <2 g/d • Light: 2-11.99 g/d • Moderate: 12-23.99 g/d • High: ≥24 g/d • Per 5 g/d increase among current drinkers	• Low: REF • **Light: 0.93 (0.90, 0.96), p<0.001** • Moderate: 1.03 (0.97, 1.09), P=0.386 • **High: 1.33 (1.19, 1.48), P<0.001** • **Per 5 g/d increase among current drinkers: 1.03 (1.02, 1.04), P<0.001**	**Key confounders:** Sex, age, SES, physical activity, smoking **Other factors considered:** anthropometry, diabetes, lipids (total cholesterol concentration, triglyceride concentration), family history of chronic disease (CHD, CVD) **Other:** marital status, resting heart rate, mental health problems	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • Individuals excluded for missing values were on average older, more likely to be male, and more likely to have died from any cause and CVD • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Evans-Polce, 2016[8] Prospective Cohort Study, National Child Development Study (NCDS) United Kingdom N= 11,469 **Participants**: All 33y at baseline; 51% female	**Baseline**: 33y **Follow-up**: 51y (18y) **Average intake:** • Abstainers: 0 units/wk reported and reported frequency as "never" (combined never + former) • ***Light drinkers (REF):*** 1-14 units/week for females; 1-21 units/week for males • Moderate drinkers: 15-28 units/week for females; 22-35 • units/week for males • Heavy drinkers: (>28 units/week for females; >35 units/week for males Unit = approximately equal to half a pint of beer (284 ml), a small glass of wine (125 ml), or a standard pub measure of distilled spirits (25 ml)	• Light drinkers: REF • Moderate drinkers: 1.09 (0.71, 1.68) • **Heavy drinkers: 1.90 (1.25, 2.88), P<0.05**	**Key confounders:** Sex, age, SES (early life social class, parent education, & home ownership; participant (adult) education & employment status), smoking, alcohol intake (at 16y, 23y) **Other factors considered:** diabetes **Other:** social support, "physical health" (heart problems, epilepsy, asthma, congenital malformations, psychiatric disorders; at 16y, 23y, 33y)	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity, alcohol pattern • Exposure measurements from baseline and earlier ages included, but no additional measurements during follow up • Exposure data measurement tool not validated • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Ferrari, 2014[9] Prospective Cohort Study, European Prospective Investigation into Cancer and nutrition (EPIC) Denmark, France, Germany, Greece, Italy, Netherlands, Spain, and United Kingdom N=349,730 **Participants**: 25-70y (~52y), 71% female; excluded entire cohorts (Naples, Italy; Bilthoven, Netherlands, Sweden, and Norway) because no information was collected on past alcohol use, and participants with incomplete vital status information, those who had not filled out dietary or lifestyle questionnaires, or whose ratio of energy intake to EER was in top or bottom 1%, those that reported cancer, diabetes, myocardial infarction, heart disease or stroke.	**Baseline**: 1992-2000 **Follow-up**: 12.6y **Average intake:** Lifetime intake: Avg of weekly consumption at ages 20, 30, 40, & 50y • Never drinkers (potentially includes never + former) • ***Moderate drinkers (REF):*** 0.1-4.9 g/d • 5-14.9 g/d • 15-29.9 g/d • Heavy drinkers: ≥30 g/d (women) or 30-59.9 g/d (men) • Extreme drinkers: ≥60 g/d (men)	**Women** 0.1-4.9 g/d (REF) 5-14.9 g/d: NS 15-29.9 g/d: NS **≥30 g/d: 1.27 (1.13, 1.43)** **Men** 0.1-4.9 g/d (REF) **5-14.9 g/d: 0.93 (0.87, 0.99)** 15-29.9 g/d: NS **30-59.9 g/d: 1.15 (1.06, 1.24)** **≥60 g/d: 1.53 (1.39, 1.68)**	**Key confounders:** Sex, age, SES, smoking, alcohol pattern **Other factors considered:** total energy intake, anthropometry, diabetes **Other:** Center; in women: menopausal status, ever use of replacement hormones, number of full-term pregnancies	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Gea, 2014[10] Prospective Cohort Study, Seguimiento Universidad de Navarra (SUN) Project Spain N=18,394 **Participants**: ~44y, 60% female; excluded participants with total daily energy intake out of percentiles 1 and 99	**Baseline**: 2009 **Follow-up**: ~12y **Average intake** Adherence to Mediterranean alcohol-drinking pattern (MADP): • Abstainers (combines never + former) • Low (0-2 pts) • Moderate-low (3-4pts) • Moderate-high (5-6pts) • ***High (7-9pts, REF)*** **Moderate alcohol intake:** • Low: 5 g/d women; <10 g/d men • Moderate: 5-25 g/d women, 10-50 g/d men • High: > 25 g/d women, >50 g/d men	**By 2pt increase in MADP score among drinkers: 0.75 (0.62, 0.89)** **Adherence to MADP:** **Low: 3.09 (1.74, 5.50)** Mod-low: NS Mod-high: NS High (REF): **Alcohol intake:** Moderate (REF) Low: NS **High: 2.07 (1.20, 3.57)** Proportion of alcohol consumed from spirits or wine was not significantly associated with mortality.	**Key confounders:** Sex, age, eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** total energy intake, anthropometry, hypertension, diabetes, beverage type (e.g., beer, wine, spirits) **Other:** Hypercholesterolemia, cancer, watching television	• **Key confounders NOT accounted for:** race/ethnicity, SES • Exposure data only measured once • Length of follow-up differs among participants • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Goulden, 2016[11] Prospective Cohort Study, Health and Retirement Study (HRS) United States N= 24,029 **Participants**: ~66y (all >50y), 58% female, 75% white, BMI ~27.4 kg/m^2	**Baseline**: 1995-2004 **Follow-up**: 2012 **Average intake:** (avg from 3 interviews over 4y prior to baseline—each interview reflects avg intake from last 3 months) • Non-drinker: abstinent over 4y; From data waves 4-7, separated into: • Lifetime non-drinker • Former drinker now abstainer • ***Occasional (REF)*:** reported drinking on at least 1 occasion, but never more than <1/wk • <7 drinks/wk • 7-<14 drinks/wk • 14-<21 drinks/wk • ≥21 drinks/wk	Full sample (N=24,029): • Occasional: REF • <7 drinks/wk: 1.02 (0.94, 1.11) • **7-<14 drinks/wk: 1.14 (1.02, 1.28)** • 14-<21 drinks/wk: 1.13 (0.93, 1.35) • **≥21 drinks/wk: 1.45 (1.16, 1.81)** *Data stratified by age & sex available in paper* Separation of non-drinker (N=8,452): • Lifetime non-drinker: 1.16 (0.95, 1.43) • **Former drinker now abstainer: 1.26 (1.05, 1.53)** • Occasional: ref • <7 drinks/wk: 0.99 (0.82, 1.21) • 7-<14 drinks/wk: 1.21 (0.91, 1.61) • 14-<21 drinks/wk: 1.30 (0.88, 1.91) • ≥21 drinks/wk: 1.49 (0.97, 2.29)	**Key confounders:** Sex, age, race/ethnicity, SES (income quintile, wealth quintile), physical activity, smoking, alcohol pattern (binge drinking) **Other factors considered:** anthropometry, hypertension, diabetes **Other:** religiosity, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level	• **Key confounders NOT accounted for:** eating pattern or diet quality • Older cohort: Survival bias • Exposure data measurement tool not validated • Different length of follow up across participants (2-12y) • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Graff-Iversen, 2013[12] Prospective Cohort Study Norway N= 12,472 **Participants**: 20-62y, 49% female	**Baseline**: 1987-1988 **Follow-up**: ~20.4y **Frequency of alcohol use:** Abstainers (REF): did not differentiate never from former drinkers, therefore data not extracted **Binge drinking:** • ***Not in the last year (REF)*** • A few times last year • 1-3 times/mo • 1-2 times/wk • ≥3 times/wk Frequency not reported	**Binge drinking:** **MEN:** • Not in the last year: REF • A few times last year: 1.14 (1.00, 1.31) • **1-3 times/mo: 1.29 (1.09, 1.52)** • **1-2 times/wk: 1.43 (1.11, 1.84)** • **≥3 times/wk: 2.68 (1.88, 3.82)** • Frequency not reported: 1.23 (0.95, 1.60) **WOMEN:** • Not in the last year: REF • **A few times last year: 1.26 (1.06, 1.50)** • **1-3 times/mo: 1.50 (1.06, 2.14)** • **≥1 time/wk: 2.06 (1.17, 3.62)** • Frequency not reported: 1.16 (0.92, 1.45)	**Key confounders:** Sex, age, SES, smoking, alcohol intake (for pattern exposure) **Other factors considered:** hypertension, blood pressure, diabetes, medications, **Other:** myocardial infarction, angina, stroke, angina symptoms, systolic blood pressure	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity • Exposure data measurement tool not validated • No preregistered data analysis plan

Hartz, 2018[13]

Prospective Cohort Study, National Health Interview Survey (NHIS) + Veterans Health Administration (VA) clinics

United States

N=340,668 (NHIS), 93,653 (VA)

Participants: NHIS: 47y, 18-85y; VA: 53y; 55% female (NHIS), 11% female (VA)

Excluded: those with missing alcohol-related data (NHIS)

Baseline: 1997-2009 (NHIS), 2008 (VA)

Follow-up: 2011 (NHIS), 2016 (VA)

Pattern of intake + frequency:

- **Frequency of non-binge drinking associated with lowest risk of ACM: 1-2 drinks ~2-3 times/wk, REF**
  - 3.2 times/wk (NHIS)
  - 2-3 times/wk (VA)
- 1-2 drinks 5 times/wk
- 1-2 drinks 6 times/wk
- 1-2 drinks 7 times/wk
- Once weekly
- Monthly
- Never drinker (NHIS)
- Former drinker (NHIS)
- Binge drinking (≥5 drinks)
  - Continuous, days/mo (NHIS)
  - Categorical (VA)
- Non-drinker (VA): does not distinguish never/former

NHIS:

Frequency of non-binge drinking

- 1-2 drinks 3.2/wk, REF
- **Frequency of drinking (non-binge) linear term: 1.04 (1.01, 1.07)**
- **Frequency of drinking (non-binge) cubic term: 1.08 (1.081, 1.082)**
- **Frequency of binge drinking linear term: 1.10 (1.09, 1.10)**
- **1-2 drinks 5/wk: 1.05 (P=0.003)**
- **1-2 drinks 6/wk: 1.12 (P<0.0001)**
- **1-2 drinks 7/wk: 1.26 (P<0.0001)**
- Once/wk: 1.04 (P=0.05)
- **Once/mo: 1.06 (P<0.01)**
- **Never: 1.24 (1.18, 1.29)**
- **Former: 1.14 (1.07, 1.22)**

Quantity of non-binge drinking

- 1-2 drinks 3.2/wk, REF
- **3-4 drinks: 1.29 (1.22, 1.37)**

Frequency of binge drinking

- 1-2 drinks 3.2/wk, REF
- **1.10 (1.09, 1.10)**

VA:

Frequency of non-binge drinking

- 1-2 drinks 2-3 times/wk, REF
- **1-2 drinks ≥4/wk: 1.23 (1.04, 1.45)**
- 1-2 drinks 2-4/mo: NS
- ≤Monthly: NS

Quantity of non-binge drinking

- Typically 1-2 drinks/occ, REF
- **Typically 3-4 drinks/occ: 1.81 (1.28, 1.56)**

Key confounders: Sex, age, race/ethnicity, SES (NHIS: education, employment status, food stamp eligibility), physical activity (NHIS), smoking (NHIS), alcohol pattern (for alcohol intake), alcohol intake (for alcohol pattern)

Other factors considered: age distribution of the study sample, diabetes

Other: Region of country, survey administration year, perceived health status, medical comorbidities

- **Key confounders NOT accounted for**: SES (VA), eating pattern or diet quality, physical activity (VA), smoking (VA)
- Exposure data measurement tool not validated (NHIS)
- Exposure data only measured once
- No information on non-completers
- No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
		Frequency of binge drinking • Never (REF) • **≤Monthly: 1.41 (1.28, 1.56)** • **Weekly: 1.79 (1.57, 2.04)** • **Daily/Almost Daily: 2.63 (2.34, 2.97)** **Secondary analyses in paper stratified by gender**		
Holahan, 2010[14] Prospective Cohort Study United States N=1,824 **Participants**: 61y (55-65y), 37% female, 91% Caucasian Excluded lifetime abstainers and those with missing data	**Baseline**: NR **Follow-up**: 20y **Average intake:** avg/wk by beverage type + frequency/wk, converted to g/d • Abstainers (0 g/d) (this group is 100% former drinkers, lifetime abstainers were excluded) • Light drinkers: consuming <1 drink/d (>0 to <14 g/d) • ***Moderate drinkers (REF):*** 1 to <3 drinks/d (14 to <42 g/d) • Heavy drinkers: ≥3 drinks/d (≥42 g/d)	• **Light: 1.12 (0.94, 1.35), P<0.05** • Moderate (REF) • **Heavy: 1.42 (1.17, 1.73), P<0.001**	**Key confounders:** Sex, age, SES, physical activity, smoking, alcohol pattern **Other factors considered:** anthropometry, hypertension, diabetes **Other:** Marital status, Other health factors (cancer, heart problems, stroke, anemia, bronchitis, kidney problems, ulcers), physical ailments, depressive symptoms, avoidance coping, number of close friends, quality of friend support	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality • Older sample: Potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Holahan, 2015[15] Prospective Cohort Study United States N=1,121 **Participants**: 61y (55-65y), 36% female, excluded those who had not consumed alcohol in the last year	**Baseline**: NR **Follow-up**: 20y Level and **pattern**: • Moderate/regular • Moderate/heavy episodic • High/regular • High/heavy episodic **Average** level of drinking, men/women: • Moderate: 1-2/0.5-1 drink/d • High: >2/>1 drink/d Pattern of drinking, men/women: • Regular: <5/<4 drinks in an occasion • Heavy episodic: ≥5/≥4 drinks in an occasion	**Level and pattern:** • High/regular, REF • High/heavy episodic: NS • Moderate/regular, REF • **High/regular: 1.73 (1.20, 2.47)** • Moderate/heavy episodic, REF • High/heavy episodic: NS Interactions with gender (NS) and baseline medical conditions were examined in the paper (drinking level was more strongly linked to mortality among regular drinkers with fewer medical conditions)	**Key confounders:** Sex, age, SES (family income, education, marital status), physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** medical conditions (cancer, diabetes, heart problems, stroke, high blood pressure, anemia, bronchitis, kidney problems, and ulcers), anthropometry **Other:** Number of close friends, quality of friend support, avoidance coping, depressive symptoms	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality • Older sample: Potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan, but clearly followed preplanned comparisons

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Horvat, 2018[16] Retrospective Cohort Study PrivMort Hungary, Russia, Belarus N=124,150 **Participants:** 35-69y, 41% female; **e**xclusions: missing data on mortality, drinking frequency, or covariates	**Baseline:** 1998 **Follow up:** 2013 **Frequency of intake**: Reported by female relative • Never drank • Former • ***≤1x/month (REF)*** • 2-4x/month • Several times/wk • Almost every day (men) **Pattern of intake:** Forms of risky drinking in paper Data on various forms of risky drinking are also available in paper	**Men** ≤1x/month (REF) Never drank • **Russia: 0.85 (0.78, 0.93)** • Belarus: 0.92 (0.83, 1.01) • Hungary: 093 (0.87, 1.00) Former • **Russia: 0.66 (0.61, 0.72)** • **Belarus: 0.59 (0.52, 0.67)** • **Hungary: 0.66 (0.59, 0.74)** 2-4x/month • **Russia: 1.38 (1.31, 1.46)** • **Belarus: 1.20 (1.13, 1.27)** • Hungary: 1.07 (0.99, 1.15) Several times/wk • **Russia: 1.85 (1.73, 1.97)** • **Belarus: 1.65 (1.52, 1.80)** • **Hungary: 1.37 (1.27, 1.48)** Almost every day • **Russia: 1.98 (1.81, 2.17)** • **Belarus: 1.85 (1.63, 2.10)** • **Hungary: 1.65 (1.52, 1.79)** **Women** ≤1x/month (REF) Never drank • **Russia: 0.91 (0.85, 0.98)** • Belarus: 1.03 (0.96, 1.12) • Hungary: 0.96 (0.86, 1.06) Former • **Russia: 0.72 (0.57, 0.90)** • **Belarus: 0.63 (0.44, 0.91)** • **Hungary: 0.66 (0.47, 0.92)** 2-4x/month • **Russia: 1.42 (1.19, 1.68)** • Belarus: 1.28 (0.99, 1.66) • **Hungary: 1.45 (1.20, 1.75)** Several times/wk • **Russia: 2.70 (2.06, 3.53)** • **Belarus: 4.02 (2.77, 5.84)** • **Hungary: 2.10 (1.71, 2.58)** Almost every day: N/A	**Key confounders:** Sex, age, SES (education, marital status), smoking **Other factors considered:** N/A **Other:** Country of residence, relation to informant, age of informant	• **Key confounders NOT accounted for**: Race/ethnicity, eating pattern or diet quality, physical activity, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Jackson, 2015[17] Prospective Cohort Study, National Health Interview Survey (NHIS) United States N=152,180 **Participants**: ~45y, 57% female, Adults aged ≥18 years; excluded participants with missing data on alcohol consumption or mortality	**Baseline**: 1997-2002 **Follow-up**: 2006 (mean 6.4y) **Pattern of intake + frequency:** • ***Never drinkers (REF):*** ≤12 drinks during lifetime • Former drinkers: ≥12 drinks in lifetime but none during previous year • Infrequent drinkers: ≥12 drinks in lifetime but never ≥12 in a single year • 1-2 drinks ≤2 days/wk (men) or 1 drink ≤2 days/wk (women) • 1-2 drinks 3-7 days/wk (men) or 1 drink 3-7 days/wk (women) • ≥3 drinks ≤2 days/wk (men) or ≥2 drinks ≤2 days/wk (women) • ≥3 drinks 3-7 days/wk (men) or ≥2 drinks 3-7 days/wk (women)	**White Men** (n=55,700) Never (REF) **Former: 1.17 (1.02, 1.35)** Infrequent: NS 1-2 drinks ≤2 d/wk: NS 1-2 drinks 3-7 d/wk: NS **≥3 drinks ≤2 d/wk: 0.84 (0.72, 0.97)** ≥3 drinks 3-7 d/wk: NS **Black Men** (n=9593) Never (REF) Former: NS Infrequent: NS 1-2 drinks ≤2 d/wk: NS 1-2 drinks 3-7 d/wk: NS ≥3 drinks ≤2 d/wk: NS **≥3 drinks 3-7 d/wk: 1.44 (1.02, 2.04)** **White Women** (n=70,669) Never (REF) Former: NS Infrequent: NS **1-2 drinks ≤2 d/wk: 0.79 (0.70, 0.88)** **1-2 drinks 3-7 d/wk: 0.71 (0.61, 0.82)** **≥3 drinks ≤2 d/wk: 0.62 (0.51, 0.76)** ≥3 drinks 3-7 d/wk: NS **Black Women** (n=16,218) Never (REF) Former: NS Infrequent: NS 1-2 drinks ≤2 d/wk: NS 1-2 drinks 3-7 d/wk: NS **≥3 drinks ≤2 d/wk: 0.53 (0.33, 0.85)** ≥3 drinks 3-7 d/wk: NS	**Key confounders:** Sex, age, race/ethnicity, SES (education, household income, marital status, poverty status, employment status), physical activity, smoking **Other factors considered:** distribution of the study sample, anthropometry **Other:** Visited health care professional, self-reported health status	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan

Jayasekara, 2015[18] Prospective Cohort Study, Melbourne Collaborative Cohort Study (MCCS) Australia N=39,577 Participants: 40-69y; 60% female Excluded those with missing alcohol intake or implausibly high intake, extreme energy intake, or missing data for any potential confounding variable	**Baseline**: 1990-1994 **Follow-up**: 2008 **Average intake (by beverage type) + frequency, converted to g/d** • ***Lifetime abstainer (REF):*** <12 drinks in any past year • >0-9 g/d • 10-19 g/d • 20-39 g/d • 40-59 g/d • 60-79 g/d • ≥80 g/d	**Men** *Average lifetime intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.83 (0.73, 0.94)** **10-19 g/d: 0.87 (0.76, 0.99)** **20-39 g/d: 0.81 (0.71, 0.92)** 40-59 g/d: NS 60-79 g/d: NS **≥80 g/d: 1.46 (1.13, 1.88)** *Usual current intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.87 (0.79, 0.97)** 10-19 g/d: NS **20-39 g/d: 0.79 (0.70, 0.90)** 40-59 g/d: NS 60-79 g/d: NS ≥80 g/d: NS *Maximum usual past intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.85 (0.74, 0.97)** **10-19 g/d: 0.83 (0.73, 0.96)** **20-39 g/d: 0.79 (0.69, 0.90)** 40-59 g/d: NS 60-79 g/d: NS **≥80 g/d: 1.26 (1.08, 1.49)** **Women** *Average lifetime intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.85 (0.77, 0.94)** 10-19 g/d: NS 20-39 g/d: NS ≥40 g/d: NS *Usual current intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.88 (0.79, 0.98)** **10-19 g/d: 0.82 (0.70, 0.95)** 20-39 g/d: NS ≥40 g/d: NS *Maximum usual past intake (g/d)* Abstainer (REF) **>0-9 g/d: 0.86 (0.77, 0.96)** **10-19 g/d: 0.85 (0.74, 0.98)** 20-39 g/d: NS ≥40 g/d: NS	**Key confounders:** Sex, age, race/ethnicity, SES (education, residential address-based measure), physical activity, smoking **Other factors considered:** total energy intake (from food), anthropometry **Other:** Household size, fruit and vegetable consumption, saturated fat	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Jung, 2012[19] Prospective Cohort Study, Korean Multi-center Cancer Cohort (KMCC) Korea N= 16,320 **Participants**: ≥20y (41% ≥60y), 61% female; excluded those with missing or no information on alcohol consumption habits, and those <20y of age	**Baseline**: 1993-2004 **Follow-up**: median 9.3y **Consumption status** • ***Never (REF)*** • Past • Current **Average intake (by beverage type) + frequency, converted to g/wk** • Never drinker • ***0.01-90 g/wk (REF)*** • 90.01-252 g/wk • 252.0-504 g/wk • >504.01 g/wk	**Consumption status** Never (REF) **Past: 1.72 (1.38, 2.14)** **Current: 1.21 (1.06, 1.39)** **Average intake (g/wk)** 0.01-90 (REF) Never drinker: NS 90.01-252 g/wk: NS 252.01-504 g/wk: NS **>504.01 g/wk: 1.39 (1.05, 1.83)**	**Key confounders:** Sex, age, race/ethnicity, SES (education), smoking **Other factors considered:** age distribution of the study sample, anthropometry **Other:** geographic area	• **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan
Kabat, 2015[20] Prospective Cohort Study, NIH-AARP Diet and Health Study United States N=476,396 Participants: 50-71y; 40% female; excluded those who had questionnaires completed by proxy respondents, had a history of cancer, died or moved out of study area before study entry, were identified as having cancer through death reports only (n = 2152), had zero follow-up time, had a log-transformed calorie intake of >3 SDs beyond mean, or were missing information needed to construct score (adherence to American Cancer Society guidelines)	**Baseline**: 1995-1996 **Follow-up**: 2009 (13.6y) **Average intake:** • ***Heavier (REF):*** ≥3 drinks/d (men); ≥2 drinks/d (women) • Never: nondrinkers (never+former) • Lighter: 1-2 drinks/d (men); 1 drink/d (women)	**Men** Heavier (REF) **Lighter: 0.91 (0.89, 0.94)** **Women** Heavier (REF) **Lighter: 0.92 (0.89, 0.96)**	**Key confounders:** Sex, age, race/ethnicity, SES, eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry **Other:** marital status	• **Key confounders NOT accounted for**: alcohol pattern • Older cohort: Potential survival bias • Exposure data only measured once • Nondrinker group likely combines never and former drinkers • No information on non-completers • Trial registry does not have data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Kerr, 2011[21] Prospective Cohort Study, National Alcohol Surveys (NAS) United States N=10,146 **Participants**: 42y, 57% female	**Baseline**: 1984, 1995 **Follow-up**: 2006 (22y) **Average intake**: • Ex-drinker • Lifetime abstainer • Occasional drinkers (0-<2/mo) • ***Moderate drinkers (REF):*** 2-<30/mo, women; 2-<60/mo, men • Heavy drinkers (30-<120/mo, women, 60->120/mo, men) • Heavy, ≥120 drinks/mo Alcohol consumption, **pattern**: • Former drinkers with no alcohol problems • Former drinkers with alcohol problems • Lifetime abstainers • Occasional drinkers, no problems • Occasional drinkers, with problems • ***Moderate drinkers (REF):*** no ≥5 drink days • Moderate drinkers, with ≥5 drink/days • Heavy drinkers, no ≥8 drink days • Heavy drinkers, with ≥8 drink days	**Consumption Volume (unadj):** • Ex-drinker: NS **(Black: 0.71 (0.56, 0.91), Hispanic: 1.44 (1.03, 2.01), White: 1.50 (1.20, 1.87)**) • Lifetime abstainer: NS • Occasional drinkers: NS • Moderate drinkers (REF) • Heavy drinkers: NS • Heavy drinkers, ≥120/mo: NS **Consumption Pattern (adj):** • Former drinkers with no alcohol problems: NS (**Black: 0.66 (0.53, 0.87); Hispanic: 1.56 (1.07, 2.27); White: 1.59 (1.25, 2.02)**) • **Former drinkers with alcohol problems: 1.58 (1.21, 2.07)** (**Black: 1.76 (1.10, 2.93)**, NS for Hispanic, White) • Lifetime abstainers: NS (**White: 1.33 (1.06, 1.68)**; NS for Hispanic, Black) • Occasional drinkers, no problems: NS (**White: 1.39 (1.09, 1.77)**; NS for Hispanic, Black) • Occasional drinkers, with problems: NS (**White: 4.28 (2.36, 7.79)**; NS for Hispanic, Black) • Moderate drinkers, no ≥5 drink days (REF) • **Moderate drinkers, with ≥5 drink/days: 1.86 (1.29, 2.69)** (**Black: 1.94 (1.16, 3.23)**, NS: for Hispanic, White) • Heavy drinkers, no ≥8 drink days: NS • Heavy drinkers, with ≥8 drink days: NS (**White: 1.98 (1.15, 3.42)**; NS for Hispanic, Black)	**Key confounders:** Sex, age, race/ethnicity, SES (education, income), alcohol intake (for pattern exposure), smoking **Other factors considered:** N/A **Other:** Region of the United States, born in the United States, depression, impulsivity scale, use of illegal drugs or cannabis	• **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity • Exposure data only measured once • No information on criteria used to select participants into the analysis or on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Keyes, 2019[22] Prospective Cohort Study, Health and Retirement Study United States N=7,904 **Participants:** ~61y (all >56y), 54% female, 73% white, 68% overweight/obese	**Baseline**: 1998 **Follow-up**: 15y **Average + Pattern** • Lifetime abstainers: <12 drinks in lifetime • Current abstainers: did not drink in the current wave, but drank in the past or we cannot rule out that they drank in the past • ***Occasional drinkers (REF)***: drinking <1 d/wk (e.g., 1-2/mo), not binging > 5 drinks in a single day for men or >4 drinks in a single day for women, and drinking a max of 3 drinks/d for men and a max of 2 drinks/d for women • Moderate drinkers: drinking 1 to 2 (women) or 1 to 3 (men) drinks ≥1 d/wk, and not binging >5 drinks in a single day for men or >4 drinks in a single day for women • Heavy drinkers: men consuming >3 drinks/d or binging >5 drinks in 1 day and for women as consuming >2 drinks/day or binging >4 drinks in 1 day	**Men** • Lifetime abstainers: 1.08 (0.87, 1.34) • **Current abstainers: 1.25 (1.02, 1.53)** • Occasional drinkers: REF • **Moderate drinkers: 0.74 (0.60, 0.91)** • Heavy drinkers: 0.97 (0.68, 1.40) **Women** • **Lifetime abstainers: 1.35 (1.08, 1.68)** • **Current abstainers: 1.34 (1.08, 1.67)** • Occasional drinkers: REF • Moderate drinkers: 0.82 (0.63, 1.07) • Heavy drinkers: 1.07 (0.54, 2.11)	**Key confounders:** Sex, age, race/ethnicity, SES (education, wealth), physical activity, smoking, alcohol pattern (def of exposure included binge drinking) **Other factors considered:** anthropometry, hypertension, blood pressure, diabetes **Other:** depressive symptoms; difficulty in activities of daily living, since previous wave: arthritis, cancer, heart disease, stroke, lung disease, psychiatric problem	• **Key confounders NOT accounted for:** eating pattern or diet quality • Older cohort: Potential survival bias • Exposure data measurement tool not validated • No preregistered data analysis plan

Knott, 2015[23]

Prospective Cohort Study, Health Survey for England

England

N= 18,368 and 34,523

Participants: ≥50y (50-64y: ~53%; ≥65y: ~47%)

~55% female

Baseline: 1998-2008

Follow-up: 2011 (Median: 6-10y)

Avg weekly consumption, 1998-2002, N=18,368:

- ***Never drinker (REF)***: reported does not drink nowadays and has always been a non-drinker
- Former drinker: reported does not drink nowadays but has not always been a non-drinker
- Not in past 12 mo: reported does drink nowadays but not in past 12 mo
- <1 occasion/mo
- 1-2 occasions/mo
- 0.1–5 units/wk
- 5.1–10 units/wk
- 10.1–15 units/wk
- 15.1–20 units/wk
- >20 units/wk

Heaviest day (of the past week), 1999-2008, N=34,523:

- ***Never drinker (REF)***
- Former drinker:
- Not in past 12 mo:
- <1 occasion/mo
- 1-2 occasions/mo
- >2 occasions/mo
- 0.1-1.5 units
- 1.6-3.0 units
- 3.1-4.5 units
- >4.5 units

Men by age: (only significant comparisons reported)

Men, 50-64y:

Weekly:

- Never drinker: REF
- **15.1–20 units/wk: 0.49 (0.26, 0.91), P=0.03**

Heaviest day:

- Never drinker: REF
- **0.1-1.5 units: 0.43 (0.21, 0.87), P=0.02**

Men, >65y:

Weekly:

- Never drinker: REF
- All NS

Heaviest day:

- Never drinker: REF
- All NS

Women by age:

Women, 50-64y:

Weekly:

- Never drinker: REF
- **Former drinker: 1.79 (1.02, 3.16), P=0.04**

Heaviest day:

- Never drinker: REF
- All NS

Women, >65y:

Weekly:

- Never drinker: REF
- **Former drinker: 1.23 (1.01, 1.51), P=0.04**
- **Not in past 12 mo: 1.72 (1.03, 2.88), P=0.04**
- **<1 occ/mo: 0.83 (0.70, 0.99), P=0.04**
- **1-2 occ/mo: 0.74 (0.60, 0.91), P=0.01**
- **0.1-5.0 units/wk: 0.77 (0.64, 0.92), P=0.01**
- **5.1–10 units/wk: 0.77 (0.63, 0.94), P=0.01**

Key confounders: Sex, age, race/ethnicity, SES (education, social class, employment status), smoking

Other factors considered: anthropometry

Other: government office region, marital status

- **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure)
- Older cohort: Potential survival bias
- Exposure data measurement tool not validated
- Exposure data only measured once
- Length of follow-up differs among participants
- No information on non-completers
- No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
		Heaviest day: • Never drinker: REF • **<1 occ/mo: 0.79 (0.66, 0.94), P=0.01** • **1-2 occ/mo: 0.70 (0.56, 0.86), P<0.01** • **0.1-1.5 units: 0.76 (0.63, 0.91), P<0.01** • **1.6-3.0 units: 0.73 (0.60, 0.90), P<0.01** • **3.1-4.5 units: 0.58 (0.39, 0.87), P=0.01** • **>4.5 units: 0.63 (0.42, 0.95), P=0.03** **Analyses including those <50y included in supplement document**		

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Kunzmann, 2018[24] Prospective Cohort Study (secondary analysis of RCT) United States N=99,654 **Participants:** 55-74y (~65y); 69% female; exclusions: cancer diagnosis or death before exposure assessment, missing data on exposure and covariates	**Baseline**: Variable (began 1998) **Follow up**: ~13y / 2009 **Average lifetime intake**: average of retrospective reports of intake at ages 18-24, 25-39, 40-54, and ≥55y: • Never: reported no intake on all assessments • Infrequent: >0-<1 drink/wk • ***Light (REF):*** 1-<3 drink/wk • Somewhat light: 3-<5 drink/wk • Light-moderate: 5-<7 drink/d • Moderate: 1-<2 drink/d • Heavy: 2-<3 drink/d • Very heavy: 3+ drink/d These frequencies take into account seasonal differences by assessing summer separately	**Men** • **Never: 1.25 (1.11, 1.40)** • **Infrequent: 1.14 (1.04, 1.24)** • Light: (REF) • Somewhat light: 0.95 (0.87, 1.05) • Light-moderate: 1.05 (0.95, 1.16) • Moderate: 1.03 (0.95, 1.13) • **Heavy: 1.19 (1.07, 1.32)** • **Very heavy: 1.36 (1.23, 1.50)** **Women** • **Never: 1.29 (1.14, 1.46)** • **Infrequent: 1.23 (1.12, 1.35)** • Light: (REF) • Somewhat light: 1.01 (0.88, 1.15) • Light-moderate: 1.10 (0.93, 1.30) • Moderate: 1.11 (0.95, 1.30) • **Heavy: 1.38 (1.07, 1.78)** • **Very heavy: 1.99 (1.51, 2.64)**	**Key confounders:** Sex, age, race/ethnicity, SES (education, marital status), smoking **Other factors considered:** total energy intake, anthropometry **Other:** Study center, randomization group, year of exposure assessment, HRT use (women), intake of red meat, processed meat, coffee, fruit, vegetable, fiber, calcium	• **Key confounders NOT accounted for**: Eating pattern or diet quality, physical activity, alcohol pattern • Older cohort: Potential survival bias • Exposure data only measured once but does include retrospective data • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Lantz, 2010[25] Prospective Cohort Study Americans' Changing Lives (ACL) longitudinal study United States N=3,617 **Participants:** ≥25y, 53% female, 84% non-Hispanic White	**Baseline**: 1986, 1989, 1994, 2001/2002 **Follow-up**: 2005 (~19y) **Average intake** (Drinks past month) • None/non-drinker (0 drinks in the past month) (cannot distinguish never from former drinkers) • ***Moderate drinkers (REF):*** 1-79 drinks the past month • Heavy drinkers (80 or more drinks in the past month)	• Moderate (REF) • Heavy: 1.13 (0.68, 1.88) Stratified by age: <55y, 55y+ • <55y, Heavy: 1.16 (0.50, 2.69) • +55y, Heavy: 1.07 (0.59, 1.96)	**Key confounders:** sex, age, race/ethnicity, SES (education, income), physical activity, smoking **Other factors considered:** age distribution of the study sample, anthropometry **Other:** residence (rural, suburban, central city), physical impairment, self-rated health	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Exposure data measurement tool not validated • No information on non-completers • No preregistered data analysis plan
Li, 2018[26] Prospective Cohort Study NHS and HPFS United States N=123,219 **Participants**: 47y (women, 30-55y) and 54y (men, 40-75y), 64% female; excluded participants who were underweight, missing data, or had implausible energy intake	**Baseline**: 1980 (women), 1986 (men) **Follow-up**: 2014 (33.9y (women), 27.2y (men)) **Avg intake** across assessments occurring every 4y • 0 g/d alcohol (likely combined never + former, not extracted) • 1-4.9 g/d alcohol • ***5-14.9 g/d alcohol, REF*** • 15-29.9 g/d alcohol • ≥30 g/d alcohol	• 1-4.9 g/d alcohol: 1.03 (1.00, 1.06) • 5-14.9 g/d alcohol (REF) • 15-29.9 g/d alcohol: 0.99 (0.96, 1.03) • **≥30 g/d alcohol: 1.25 (1.19, 1.30)**	**Key confounders:** Sex, age, race/ethnicity **Other factors considered:** medications (current multivitamin use; current aspirin use), family history of diabetes mellitus, myocardial infarction, or cancer **Other:** menopausal status and hormone use (women only)	• **Key confounders NOT accounted for**: SES, eating pattern or diet quality, physical activity, smoking, alcohol pattern • Not clear if the "0 g/d" group included both never and former drinkers • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Licaj, 2016[27] Prospective Cohort Study, Swedish Women's Lifestyle and Heath cohort Sweden N= 33,404 **Participants**: ~41y (30-49y), 100% female	**Baseline**: 1991-1992 **Follow-up**: 2012 (~20y) **Average intake:** • 0 g/d: abstainers (not extracted because combines never and former drinkers) • ***"Light" (REF):*** 0.1–1.49 g/day • 1.5–4.9, g/day • 5–9.9 g/day • 10–14.9 g/day • 15+ g/day **Change from 1991-2004:** • ***Maintain low (REF):*** <5g/d • Stop drinking • Start drinking • Never at both times • Maintain high, ≥5g/d • Increased from <5 to ≥5g/d • Decreased from ≥5 to <5g/d	Average intake: HR (95% CI) NS Change from 1991-2004: • Maintain low, <5g/d: Ref • **Stop drinking: 1.49 (1.10, 2.02)** • Start drinking: 1.17 (0.92, 1.48) • **Never at both times: 1.53 (1.20, 1.96)** • Maintain high, ≥5g/d: 1.00 (0.84, 1.18) • Increased from <5 to ≥5g/d: 0.82 (0.68, 1.00) • Decreased from ≥5 to <5g/d: 1.17 (0.89, 1.54)	**Key confounders:** Sex, age, SES (education), physical activity, smoking **Other factors considered:** energy intake not from alcohol, anthropometry, family history of chronic disease (breast cancer) **Other:** number of children, age at first birth, oral contraceptive use and duration, menopausal status at baseline and age at menopause	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Exposure data measurement tool not validated • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Lindshou Hansen, 2011[28] Prospective Cohort Study Diet, Cancer, and Health study Denmark N=55,462 **Participants:** 50-64y (~56y); 53% female; eligible participants were born in Denmark and had no previous cancers; excluded participants with missing information on relevant questionnaire data, acute coronary syndrome (ACS) diagnosis before baseline or were registered with ACS diagnosis during follow-up, whose medical record could not be retrieved and whose endpoint could not be validated	**Baseline**: 1993-1997 **Follow-up**: 7.6y **Average intake:** drinks / week • <1 (never+former combined) • ***1-6 (REF)*** • 7-13 • 14-20 • 21-27 • 28-34 (men) or ≥28 (women) • ≥35	HR reported in figure only and stratified by those with and without hypertension (Figure 2). Text states: "All-cause mortality risk according to alcohol intake was J-shaped in men and women (data not shown). In analyses including hypertension, the association between alcohol and risk of mortality was also J-shaped and the risk among participants with hypertension was higher than for participants without hypertension at all levels of alcohol intake (Figure 2)."	**Key confounders:** Sex, age, SES (education), eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry, hypertension, diabetes **Other:** hypercholesterolemia; for women: menopausal status and use of hormone replacement therapy	• **Key confounders NOT accounted for**: race/ethnicity, alcohol pattern • Older cohort: Potential survival bias • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan
Luksiene, 2017[29] Prospective Cohort Study, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Lithuania N=6,729 **Participants:** 35-64y, 52% female; excluded those with incomplete information on analyzed covariates; women not included in multivariate analysis due to small numbers of events, and current smokers and drinkers	**Baseline:** 1983-2002 **Follow-Up:** 21y **Average intake** • ***None (REF):*** likely combined never + former • ***1-14 units/wk (REF)*** • >14 units/wk	**Men** 1-14 units/wk (REF) **>14 units/wk: 1.34 (1.13, 1.59)** **Women** 1-14 units/wk (REF) >14 units/wk: 0.64 (0.24, 1.70) **Multivariate analysis in men by smoking status are in the paper.**	**Key confounders:** Sex **Other factors considered:** N/A **Other:** N/A	• **Key confounders NOT accounted for**: age, race/ethnicity, SES, eating pattern or diet quality, physical activity, smoking, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Lundin, 2015a[30] Prospective Cohort Study, Vietnam Experience Study (VES) United States N= 4,462 **Participants**: **Vietnam-era Army Vets**: mean 38.3y (31.1-49.0y), 0% female; Alcohol use disorder prevalence: 46.7% Inclusion criteria were: (1) entering military service between January 1, 1965 and December 31, 1971; (2) served only one term of enlistment; (3) served at least 16 weeks of active duty; 4) earned a military specialty other than "trainee" or "duty soldier" and at discharge from active duty had a military paygrade no higher than sergeant	**Baseline**: 1985 **Follow-up**: 2000 **Average intake:** ***1-7 drinks/wk (REF)*** 8-10 drinks/wk 10-14 drinks/wk 15-28 drinks/wk ≥29 drinks/wk Non-drinkers (does not distinguish between never and former; data not extracted) **Binge frequency:** ***Drinker, non-binger (REF)*** 1-3/mo 4-7/mo 8-15/mo ≥16/mo Non-drinkers (does not distinguish between never and former; data not extracted)	*Average intake:* 1-7 drinks/wk: REF All NS *Binge frequency*: Drinker, non-binger: REF All NS	**Key confounders:** Sex, race/ethnicity, SES (education, marital status), smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** N/A **Other:** depressive disorder, antisocial personality disorder	• **Key confounders NOT accounted for**: age, eating pattern or diet quality, physical activity • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Lundin, 2015b[31] Prospective Cohort Study, REBUS Sweden N= 1,895 **Participants**: 18–65y, 18-25y: 14%; 26-35y: 20%; 36-45y: 16%; 46-55y: 22%; 56-65y: 29%; 51% female	**Baseline**: 1969-1970 **Follow-up**: 2011 (41-42y) **Average intake: Frequency + amount per occasion** • Lifetime abstainer • Former drinker • ***Low consumption (REF):*** 1-49g/wk • Moderate consumption: 50-139 g/wk • High consumption: ≥139 g/wk	• Lifetime abstainer: 0.83 (0.59, 1.18) • **Former drinker: 1.86 (1.27, 2.73)** • Low consumption: REF • Moderate consumption: 0.89 (0.72, 1.10) • High consumption: 1.01 (0.76, 1.35)	**Key confounders:** Sex, age, SES (social class, school level, marital status); Note: Age controlled for in 5 groups: 18-25, 26-35, 36-45, 46-55, and 56-65 years **Other factors considered:** N/A **Other:** marital status, depressive neurosis, illicit substance use disorder, psychopathic personality disorder	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Exposure data measurement tool not validated • Exposure data only measured once • No preregistered data analysis plan
McCullough, 2011[32] Prospective Cohort Study, Cancer Prevention Study II (CPS-II) Nutrition Cohort United States N=111,966 **Participants:** 50-74y (~63y); 55% female; 98% White; excluded participants from analysis if they reported a history of cancer (except nonmelanoma skin cancer), myocardial infarction, or stroke; an extreme value for height or weight, and below-normal weight (BMI <18.5 kg/m^2); current smokers and individuals with missing information on smoking, physical activity, and alcohol use or who poorly completed FFQ.	**Baseline**: 1992-1993 **Follow-up**: 2006 (~14y) **Average intake:** • Nondrinker (likely never+former combined) • ≤2 drinks/d (men); ≤1 drink/d (women) • ***>2 drinks/d (men); >1 drink/d (women) (REF)***	**Men** >2 drinks/d (REF) **≤2 drinks/d: 0.86 (0.81, 0.92)** **Women** >1 drinks/d (REF) ≤1 drinks/d: 0.99 (0.11, 1.08)	**Key confounders:** Sex, age, race/ethnicity, SES (education), eating pattern or diet quality, physical activity, smoking **Other factors considered:** total energy intake, anthropometry, medications (nonsteroidal anti-inflammatory drug use) **Other:** multivitamin use, menopausal hormone therapy	• **Key confounders NOT accounted for**: Alcohol pattern • Older cohort: Potential survival bias • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Midlov, 2016[33] Prospective Cohort Study, Women's Health in Lund Area (WHILA) Sweden N=6,353 **Participants**: 50-59y, 100% female; excluded those with missing data on explanatory variables	**Baseline**: 1995-2000 **Follow-up**: 2015 (~17y) **Average intake:** • None (never+former) • ***0.1-11.9 g/d (REF)*** • ≥12 g/d	• 0.1-11.9 g/d (REF) • **≥12 g/d: 1.49 (1.18, 1.89)**	**Key confounders:** Sex, age, SES (education, marital status), physical activity, smoking **Other factors considered:** anthropometry, diabetes **Other:** marital status, ischemic heart disease	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol pattern • Older sample: potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan
Muller, 2016[34] Prospective Cohort Study, European Prospective Investigation into Cancer and Nutrition (EPIC) Denmark, France, Germany, Greece, Italy, The Netherlands, Spain, Sweden, and the United Kingdom N=246,906 **Participants**: 50y (40-50y: 25%; 50-60y: 47%; 60-70y: 24%), 65% female, excluded participants who were ≥75 or <40 years old, and those with missing questionnaire information, blood pressure measurements, or follow-up information	**Baseline**: 1992-2000 **Follow-up**: 2008-2010 (~11.5y) **Average intake:** • 0 drinks/d (never+former) • 0-0.5 drinks/d • ***0.5-1 drinks/d (REF)*** • 1-2 drinks/d • 2-6 drinks/d • >6 drinks/d (women), 6-10 drinks/d (men) • >10 drinks/d (men)	**Total Sample** • **0-0.5: 1.17 (1.10, 1.25)** • 0.5-1 drinks/d (REF) • 1-2: 0.97 (0.91, 1.04) • 2-6: 1.07 (1.00, 1.14) • **>6 (women), 6-10 (men): 1.51 (1.38, 1.66)** • **>10 (men): 2.47 (2.12, 2.88)** **Men** • **0-0.5: 1.26 (1.14, 1.38)** • 0.5-1 drinks/d (REF) • 1-2: 0.97 (0.89, 1.07) • 2-6: 1.04 (0.96, 1.14) • **6-10: 1.48 (1.32, 1.65)** • **>10: 2.43 (2.07, 2.85)** **Women** • **0-0.5: 1.13 (1.04, 1.22)** • 0.5-1 drinks/d (REF) • 1-2: 0.98 (0.90, 1.08) • **2-6: 1.16 (1.05, 1.27)** • **>6: 1.72 (1.38, 2.15)**	**Key confounders:** Sex, age, eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry, blood pressure **Other:** Country of recruitment	• **Key confounders NOT accounted for**: race/ethnicity, SES, alcohol pattern • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Ortolá, 2019[35] Prospective Cohort Study ENRICA Spain N=3,045 **Participants:** ≥60y (21% ≥75y), 54% female; excluded participants without information on alcohol consumption, missing data on confounders, and those who died in first year of follow-up	**Baseline:** 2008-2010 **Follow-up**: median 7.8y (assessed in 2012, '15, and '17) **Average intake and pattern**: • Continuous (standard units/d) • ***Never drinker (REF):*** 0 g/d • Ex-drinker: 0 g/d and answered "I used to drink alcohol, but I quit" • Occasional drinker: >0-<1.43 g/d (~1 drink/wk) • Light drinker: men ≥1.43-<20 g/d, women ≥1.43-<10 g/d, • Moderate drinker: men ≥20-<40 g/d, women ≥10-<24 g/d • Heavy/binge drinker: men ≥40 g/d, women ≥24 g/d and/or ≥80g (men) or ≥60g (women) in 1 drinking session during the past 30 days **Lifetime consumption (per decade) was also assessed and used to reclassify consumption category in separate analysis.**	*By baseline alcohol consumption* Never (REF), HR (95% CI) **Ex-drinker: 1.49 (1.03, 2.14), P<0.05** Occasional: NS Light: NS Moderate: NS Heavy/binge: NS P for trend (excluding ex-drinkers): NS *By lifetime alcohol consumption* Never (REF) Occasional: NS Light: NS Moderate: NS **Heavy/binge: 1.85 (1.07, 3.23)** P for trend: NS *By lifetime alcohol consumption, with occasional drinkers as reference:* NS for all *Change per alcohol standard unit/d:* Baseline intake: NS Cumulative intake: NS *By wine consumption among drinkers:* NS	**Key confounders:** Sex, age, SES (education), diet quality (Mediterranean Diet Adherence Screener excluding wine component), physical activity, smoking, alcohol pattern **Other factors considered:** anthropometry, hypertension, blood pressure, medications **Other:** Time watching TV and other sedentary behaviors, morbidity (diagnosed previously with CVD, cancer, chronic respiratory disease, osteomuscular disease, or depression requiring treatment), self-rated health, functional limitations in IADL	• **Key confounders NOT accounted for**: race/ethnicity • Exposure assessed at baseline only but did assess lifetime consumption retrospectively at that point • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Pan, 2019[36] Prospective Cohort Study Singapore Chinese Health Study (SCHS) Singapore N=44,052 **Participants:** ~55y (45-74y), 55% female; excluded: participants with a history of invasive cancer (except nonmelanoma skin cancer), coronary heart disease, stroke, diabetes at baseline, whose weight or height data were missing, with extreme energy intakes (<600 or >3,000 kcal for women; <700 or >3,700 kcal for men), and those without information of menopausal status at recruitment	**Baseline:** 1993-1998 **Follow up**: 12/2016 **Average intake:** • ***Healthy (REF):*** light to moderate drinking ○ Men: >0 to ≤14 drinks/wk ○ Women: >0 to ≤7 drinks/wk • Heavy ○ Men: >14 drinks/wk ○ Women: >7 drinks/wk • Light to moderate vs. Heavy	• Light to moderate (REF) • **Heavy: 1.38 (1.25, 1.53)**	**Key confounders:** Sex, age, race/ethnicity, SES (education, marital status), eating pattern or diet quality (AHEI score), physical activity, smoking **Other factors considered:** total energy intake, age distribution of the study sample, diabetes **Other:** Year of interview, marital status, sleep duration, menopausal status (women)	• **Key confounders NOT accounted for**: pattern of alcohol intake • Older cohort: Possible survival bias • Exposure data collection tool not validated • Exposure not well-defined: frequency not amount • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Perreault, 2017[37] Prospective Cohort Study Health Survey for England (HSE) and Scottish Health Survey (SHS) United Kingdom N=36,370 **Participants**: ~56y (>40y), NR% female, excluded those with missing data	**Baseline**: 1994-8-9, 2003-4-6 (HSE), 1998, 2003 (SHS) **Follow-up**: 2009 (HSE), 2011 (SHS) (353,049 person-years follow-up) **Average intake:** • ***Never drunk alcohol, REF*** • Ex-drinkers • Occasional drinkers • Within guidelines (<14 units/wk (women); <21 (men)) • Hazardous (14–35 units/wk • (women); 21–49 (men)) • Harmful (>35 (women); >49 (men))	• Never drunk alcohol, REF: 1.00 • **Ex-drinkers: 1.37 (1.21, 1.55)** • **Occasional drinkers: 0.83 (0.74, 0.94)** • **Within: 1.13 (1.02, 1.24)** • **Hazardous: 1.19 (1.06, 1.35)** • **Harmful: 1.64 (1.38, 1.95)** • **P<0.001** Results were similar, but attenuated among those who meet physical activity requirements	**Key confounders:** Sex, age, race/ethnicity, SES, physical activity, smoking **Other factors considered:** BMI **Other:** Psychological distress/depression score, CVD, cancer	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, alcohol intake (for pattern exposure) • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan
Plunk, 2014[38] Prospective Cohort Study National Health Interview Survey (NHIS) United States N=128,203 **Participants**: 18-64y (24% >50y), 48% female	**Baseline**: 1997-2001 **Follow-up**: 2006 **Pattern of intake:** • ***Lifetime abstainers (REF):*** <12 drinks in lifetime • Past-year abstainer status (12+ drinks in lifetime, but none in past year) • Heavy drinking days (# of days w/ 5+ drinks were consumed) • Non-heavy drinking days (total # of drinking days minus heavy drinking days)	Lifetime abstainers = REF **Non-heavy drinking frequency: B= -0.278, SE= 0.063, P<0.001** **Heavy drinking frequency: B=0.084, SE=0.015, P<0.001**	**Key confounders:** Sex, age, race/ethnicity, SES, smoking, alcohol intake (for pattern exposure) **Other factors considered:** anthropometry **Other:** Survey wave, census region, poor health status	• **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity • No information provided regarding criteria used to select participants into the analysis • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Powell, 2020[39] Prospective Cohort Study UK Biobank United Kingdom N= 297,988 **Participants**: ~56y (40-69y), ~57% female; excluding those with major cardiovascular event or diagnosed with cancer prior to baseline; participants with missing data in covariates included in the analyses or implausible values of sedentary behavior	**Baseline**: 2006-2010 **Follow-up**: 2016 (6-10y) **Average intake:** • ***Never drinker (REF)*** • Previous-drinkers • Within guidelines: <14 UK units alcohol/wk • Above guidelines: ≥14 and <28 UK units alcohol/wk • Double the guidelines or more: ≥28 UK units alcohol/wk 1 unit = 8g ETOH	• Never drinker: REF • **Previous drinkers: 1.41 (1.21, 1.63)** • **Within guidelines: 0.83 (0.73, 0.93)** • Above guidelines: 0.91 (0.80, 1.03) • **Double guidelines: 1.22 (1.06, 1.40)** • **P<0.001** **Interactions between alcohol intake and physical activity level are presented in the paper.**	**Key confounders:** Sex, age, SES (Townsend deprivation index), physical activity, smoking **Other factors considered:** anthropometry **Other:** Daily fruit and vegetable consumption, sedentary behavior, baseline hypertension and baseline diabetes	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, smoking, alcohol pattern (for intake exposure) • Exposure data collection methods NR • Exposure data only measured once • No preregistered data analysis plan
Rhee, 2012[40] Prospective Cohort Study Seoul Male Cohort Study Korea N=14,205 **Participants**: ~50y (40-59y), 100% male; Criteria for eligible population were males aged 40 to 59 years, residing in or near Seoul, who were beneficiaries of the Korea Medical Insurance Corporation, and who were confirmed to be disease-free at a biennial health checkup conducted in 1990 (excluded those with cancer, CVD, or myocardial infarction)	**Baseline**: 1992 **Follow-up**: 1993-2008 **Neither average nor pattern** • ***Never (REF)*** • Former • Current	• Never (REF) • Former: NS • **Current: 1.40 (1.07, 1.83)**	**Key confounders:** Sex, age, race/ethnicity, SES (education), physical activity, smoking **Other factors considered:** age distribution of the study sample, anthropometry, hypertension, diabetes **Other:** sleep hours	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Ricci, 2020[41] Prospective Cohort Study NHANES United States N=34,672 **Participants**: ~47y (≥18y), 52% female; excluded participants with missing information on mortality status, alcohol use, and covariates	**Baseline**: 1999-2014 **Follow-up**: 2015 (~7.8y) **Average intake**, g/d: • <0.1 • ***0.1 to <14, REF*** • 14 to <28 • ≥28 **Pattern of intake**, drinks/d: • ***1, REF*** • 2 • 3 • ≥4 Consuming alcohol in excess of the 2015-2020 DGAs: <u>Men:</u> • Mean alcohol intake >28 g/d (2 standard drinks) • >2 drinks during a drinking day • >1 drink during a drinking day <u>Women:</u> • Mean alcohol intake >14 g/d (1 standard drink) • >1 drink during a drinking day	**<u>MEN:</u>** Average intake, g/d: • **<0.1: 1.40 (1.20, 1.63)** • 0.1 to <14: REF • 14 to <28: 1.17 (0.94, 1.46) • **≥28: 1.55 (1.23, 1.96)** Pattern of intake, drinks/d: • 1: REF • 2: 0.83 (0.69, 1.00) • 3: 0.96 (0.76, 1.21) • **≥4: 1.34 (1.18, 1.53)** Alcohol intake >28 g/d: **HR: 1.87 (1.52, 2.30); PAR: 8.8 (5.5, 12.6)** >2 drinks during a drinking day: **HR: 1.39 (1.24, 1.55), PAR: 19.2 (12.8, 25.1)** >1 drink during a drinking day: **HR: 1.17 (1.04, 1.33); PAR: 13 (3.4, 22.3)** **<u>WOMEN:</u>** Average intake, g/d: • **<0.1: 1.21 (1.01, 1.44)** • 0.1 to <14: REF • **14 to <28: 1.34 (0.95, 1.87)** • **≥28: 1.38 (1.05, 1.83)** Pattern of intake, drinks/d: • 1: REF • 2: 1.16 (0.93, 1.44) • 3: 1.38 (0.96, 1.98) • **≥4: 1.59 (1.38, 1.83)** Alcohol intake >14 g/d: **HR: 1.47 (1.16, 1.85); PAR: 5.5 (1.9, 9.5)** >1 drink during a drinking day: **1.49 (1.30, 1.71); PAR: 25.8 (17.6, 33.5)**	**Key confounders:** Sex, age, race/ethnicity, SES, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** Energy intake, BMI, systolic and diastolic blood pressure, CVD (CAD, CHF, MI, stroke), cancer **Other:** Dietary fiber, survey	• **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Rosella, 2019[42] Prospective Cohort Study Canadian Community Health Survey (CCHS) Canada N=149,262 **Participants**: 45y (all ≥18y), 54% female; excluded participants <18y at baseline, pregnant women, death before baseline date	**Baseline**: 2000 **Follow-up**: 2015 (mean ~5.7y) **Average intake (except 'heavy' category, which combines avg + pattern)** • ***Light (REF):*** ○ Men: 1-3 drinks/wk ○ Women: 1-2 drinks/wk • Moderate: ○ Men: 4-21 drinks/wk ○ Women: 3-14 drinks/wk • Heavy: ○ Men: ≥21 drinks/wk or bingeing behavior on weekly basis (≥5 drinks/occasion) ○ Women: ≥14 drinks/wk or bingeing behavior on weekly basis (≥5 drinks/occasion) • Nondrinker: no alcohol in last 12mo or drinks <weekly (*combines former & never, so data were not extracted*)	**<u>All-Cause Mortality</u>** ***Male:*** Light (16% of male sample), REF **Moderate (25%): 0.85 (0.78, 0.93)** Heavy (12%): 1.08 (0.95, 1.23) ***Female:*** Light (11% of female sample), REF Moderate (17%): 0.94 (0.83, 1.06) **Heavy (4%): 1.56 (1.29, 1.90)** **<u>Premature Mortality (<75y)</u>** ***Male:*** Light = REF Moderate: 0.99 (0.81, 1.22) Heavy: 0.91 (0.73, 1.13) ***Female:*** Light = REF Moderate: 0.93 (0.71, 1.21) Heavy: 1.05 (0.65, 1.69) **Data are also presented on amenable vs. nonamenable deaths in the paper.**	**Key confounders:** Sex, age (ACM analysis only), SES (household income), physical activity, smoking, alcohol pattern **Other factors considered:** ADG score (likely included hypertension, blood pressure, diabetes, glucose, lipids) **Other:** N/A	• **Key confounders NOT accounted for**: Race/ethnicity, eating pattern or diet quality • Validity of exposure assessment tool unclear • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Rostron, 2012[43] Prospective Cohort Study National Health Interview Survey (NHIS) United States N=237,859 **Participants**: >18y, NR% female Excluded those with missing data	**Baseline**: 1997-2004 **Follow-up**: 2006 **Average intake**: • Never drinker (<12 drinks in life) • Former drinker (0 drinks during last year) • ***Infrequent drinker (REF):*** <12 drinks in any year • Light drinker (1 drink per drinking day), occasional or regular • Moderate drinker (2 drinks/d), occasional or regular • Heavy drinker (3+ drinks/d), occasional or regular	**Males** • Never: NS • **Former: 1.24 (1.08, 1.43)** • Infrequent (REF) • Light: NS • Occasional light: NS • Regular light: NS • Moderate: NS • Occasional moderate: NS • Regular moderate: NS • Heavy: NS • Occasional heavy: NS • **Regular heavy: 1.31 (1.12, 1.54)** **Females** • **Never: 1.34 (1.19, 1.50)** • **Former: 1.40 (1.25, 1.57)** • Infrequent (REF) • Light: NS • Occasional light: NS • Regular light: NS • Moderate: NS • **Occasional moderate: 0.86 (0.74, 0.99)** • **Regular moderate: 1.35 (1.09, 1.67)** • **Heavy: 1.19 (1.02, 1.40)** • Occasional heavy: NS • **Regular heavy: 1.61 (1.29, 2.02)**	**Key confounders:** Sex, age, race/ethnicity, SES, smoking **Other factors considered:** health status, anthropometry **Other:** N/A	• **Key confounders NOT accounted for**: eating pattern or diet quality, physical activity, alcohol intake • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Rundberg, 2014[44] Prospective Cohort Study, Women's Health in Lund Area (WHILA) Sweden N=6917 **Participants**: 50-59y, 100% female	**Baseline**: 1995-2000 **Follow-up**: 2009 **Average intake:** • Non-drinkers (0g, 0 drinks per wk), combines never + former • ***Moderate Drinkers (REF):*** 1–108 g, <9 drinks/wk • Risk drinkers (>109 g, >9 drinks/wk)	• Moderate drinker (REF) • Risk drinker: NS	**Key confounders:** Sex, age, SES, smoking, alcohol intake **Other factors considered:** hypertension, diabetes, medications **Other:** Social network, household composition, regular medical control for physical or mental disease	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity • No information provided regarding criteria used to select participants into the analysis • Exposure data measurement tool not validated • Not clear if the "non-drinkers" group included both never and former drinkers • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan
Schoenborn, 2014[45] Prospective Cohort Study, National Health Interview Survey (NHIS) United States N= 140,741 **Participants**: adults, current drinkers (participant characteristics NR)	**Baseline**: 1997-2004 **Follow-up**: 2006 **Current average drinking:** • ***Infrequent/light (REF):*** ≤3 drinks per week • Moderate: 3-7 drinks per week, women; 3-14 drinks per week, men • Heavier: >7 drinks per week, women; >14 drinks per week, men **Episodic heavy drinking:** • **<3d of 5+ drinks in the past year: REF** • ≥3d of 5+ drinks in past year	<u>Current average drinking</u> • Infrequent/light: REF • Moderate: 0.94 (0.87, 1.03) • **Heavier: 1.34 (1.17, 1.53), P<0.001** <u>Episodic heavy drinking</u> • <3d of 5+ drinks: REF • **≥3d of 5+ drinks: 1.12 (1.00, 1.26), P<0.05** • Interactions NS	**Key confounders:** Sex, age, race/ethnicity, SES (education), eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** anthropometry **Other:** N/A	• **Key confounders NOT accounted for**: eating pattern or diet quality • Participant characteristics NR • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan

Schutte, 2020[46] Prospective Cohort Study UK Biobank study United Kingdom N=446,439 (N=176,950 beer/cider N=183,930 champagne/white wine N=222,192 red wine N=125,400 spirits) **Participants**: 56y (40-69y), 54% female; excluded participants that had a previous fatal or non-fatal cardiovascular event or previous cancer diagnosis	**Baseline**: 2006-2010 **Follow-up**: 2015-2016 (~7y) **Average intake:** • Continuous (per week) • Categorical ○ ***Other alcohol drinkers (REF):*** drinkers that do not drink type of drink stipulated ○ 1-7/wk ○ 8-14/wk ○ 15-21/wk ○ >21/wk **Unit of Measure** • Beer/cider: pint (20.17 g ethanol) • Champagne/white wine: glass (11.35 g ethanol) • Red wine: glass (12.82 g ethanol) • Spirits: measures (7.89 g ethanol)	**Beer/cider** For number of weekly pints: **1.56 (1.45, 1.68), P<0.0001** Adj for total baseline alcohol **1.70 (1.53, 1.89), P<0.0001** Other alcohol drinkers (REF) 1-7/wk: 0.96 (0.90, 1.02) **8-14/wk: 1.26 (1.15, 1.37)** **15-21/wk: 1.43 (1.28, 1.60)** **>21/wk: 2.19 (1.93, 2.49)** **P-trend<0.0001** ***By weekly pint, risk becomes significantly higher at ≥5 pints/wk (supplemental tables S7 and S8)*** **Champagne/white wine** For number of weekly glasses: 1.04 (0.95, 1.14) Adj for total baseline alcohol 0.97 (0.87, 1.09) Other alcohol drinkers (REF) **1-7/wk: 0.82 (0.78, 0.86)** **8-14/wk: 0.84 (0.76, 0.94)** **15-21/wk: 0.80 (0.66, 0.96)** **>21/wk: 1.27 (1.03, 1.57)** **P-trend<0.0001** ***By weekly serving, risk becomes significantly lower at 4-5 servings/wk only*** **Red wine** For number of weekly glasses: 0.95 (0.88, 1.03)	**Key confounders:** Sex, age, SES (Townsend deprivation index), physical activity, smoking, total alcohol intake (g, in analyses labeled 'adj for total baseline alcohol') **Other factors considered:** anthropometry, blood pressure, diabetes, previous cardiovascular event or cancer, beverage type (e.g., beer, wine, spirits) **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
		Adj for total baseline alcohol **0.81 (0.73, 0.89), P<0.0001** Other alcohol drinkers (REF) **1-7/wk: 0.71 (0.67, 0.74)** **8-14/wk: 0.66 (0.61, 0.72)** **15-21/wk: 0.60 (0.52, 0.68)** **>21/wk: 0.70 (0.59, 0.84)** **P-trend<0.0001** ***By weekly serving, risk is not significant at any single level*** **Spirits** For number of weekly measures: **1.47 (1.35, 1.60), P<0.0001** Adj for total baseline alcohol **1.47 (1.35, 1.60), P<0.0001** Other alcohol drinkers (REF) 1-7/wk: 0.96 (0.92, 1.01) **8-14/wk: 1.12 (1.00, 1.25), P<.05** **15-21/wk: 1.28 (1.07, 1.53)** **>21/wk: 1.78 (1.55, 2.04)** **P-trend<0.0001** ***By weekly serving, risk becomes significantly higher at ≥7 servings/wk*** **Data also presented on single increments per week of pints, glasses and measures.**		

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Shuval, 2012[47] Prospective Cohort Study, Cooper Center Longitudinal Study (CCLS) United States N=29,402 **Participants**: 43y (20-79y), 0% female; excluded those with diabetes, myocardial infarction, hypertension, stroke, cancer, or with ECG abnormalities, missing data, died during 1st year of f/u	**Baseline**: 1993-2006 **Follow-up**: 2011 (~17.4y) **Average intake**, drinks/wk: • Nondrinkers (0) (combined never + former) • Light drinkers (<3) • Moderate drinkers (3–14) • ***Heavy drinkers (REF):*** >14	• Light: 0.88 (0.75, 1.02) • Moderate: 1.0 (0.89, 1.12) • Heavy (REF) Linear, P-trend=0.1396 Curvilinear, P-trend=0.010	**Key confounders:** Sex, age, physical activity, smoking **Other factors considered:** anthropometry (BMI), hypertension, blood pressure, diabetes, glucose, lipids **Other:** Examination year	• **Key confounders NOT accounted for**: race/ethnicity, SES, eating pattern or diet quality, alcohol intake • Selection into the analysis was based on characteristics potentially associated with the exposure and outcome • Exposure data measurement tool not validated • Exposure data only measured once • Non-drinkers likely included never and former drinkers • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Simpson, 2016[48] Prospective Cohort Study Women's Health Initiative Program (WHI) United States N= 145,521 **Participants:** 64y (50-79y), 100% female, 2.6% Veterans Women eligible to participate if they were postmenopausal, planned to remain in the area, did not report having been excessive drinker in past 5 years (i.e., (a) self-evaluated "excessive drinker," (b) had consumed equivalent of a fifth of liquor in 1 day, or (c) had ≥ 2 weeks of drinking ≥7/d), did not report needing to use more drugs to feel desired effects, did not report serious emotional problems that would interfere with study participation, and had an estimated survival of at least 3 years.)	**Baseline**: 1993-1998 **Follow-up**: 2014 (16-21y) **Average intake:** • ***Lifelong abstainers (REF):*** consumed alcohol <12 occasions in life • Former drinkers: drank in past but no longer drinking • Infrequent drinkers: <1/wk • ***Moderate drinkers (REF):*** 1-7/wk • Moderately heavy drinkers: 8-14/wk • Heavy: ≥15/wk	Veterans (n=3,719) • Lifelong abstainer (REF) • Former: NS • <1/wk: NS • 1-7/wk: NS • 8-14/wk: NS • ≥15/wk: NS • Lifelong abstainer: NS • **Former: 1.26 (1.07, 1.48)** • <1/wk: NS • 1-7/wk (REF) • 8-14/wk: NS • ≥15/wk: NS Non-Veterans (n=141,802) • Lifelong abstainer (REF) • **Former: 1.06 (1.02, 1.11)** • **<1/wk: 0.84 (0.80, 0.88)** • **1-7/wk: 0.80 (0.76, 0.83)** • **8-14/wk: 0.79 (0.74, 0.85)** • **≥15/wk: 0.91 (0.85, 0.98)** • **Lifelong abstainer: 1.26 (1.20, 1.32)** • **Former: 1.34 (1.29, 1.39)** • **<1/wk: 1.05 (1.01, 1.09)** • 1-7/wk (REF) • 8-14/wk: NS • **≥15/wk: 1.15 (1.08, 1.23)**	**Key confounders:** Sex, age, race/ethnicity, SES (income, education, marital status), physical activity, smoking **Other factors considered:** N/A **Other:** Veteran status, WHI study arm	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern • Older cohort: Potential survival bias • Exposure data only measured once • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Skov-Ettrup, 2011[49] Prospective Cohort Study Danish National Cohort Study (DANCOS) Denmark N=26,786 **Participants**: ~45y (19-75y), 51% female; excluded participants diagnosed with ischemic heart disease at baseline, and subjects without information on alcohol intake or covariates were excluded prior to analysis	**Baseline**: 1994, 2000, 2005 **Follow-up**: 6.9y Only moderate and light drinkers were included in this study (≤21 drinks/wk for men; ≤14 drinks/wk for women) <u>Drinking frequency</u> • Nondrinkers (never+former) • **1-2 days/wk (REF)** • 3-4 days/wk • 5-6 days/wk • 7 days/wk <u>Drinking pattern</u> • Nondrinkers (never+former) • **Non-binge pattern (REF):** ≤5 drinks on all drinking days) • Binge pattern (>5 drinks any drinking day) 1 Unit = 12g ETOH	**<u>Men</u>** *Drinking frequency* 1-2 days/wk, REF 3-4 days/wk: NS 5-6 days/wk: NS 7 days/wk: NS *Drinking pattern* **Nondrinkers: 1.27 (1.04, 1.56)** Non-binge: REF **Binge: 0.74 (0.57, 0.97)** **<u>Women</u>** *Drinking frequency* 1-2 days/wk, REF 3-4 days/wk: NS 5-6 days/wk: NS 7 days/wk: NS *Drinking pattern* Non-binge: REF Binge: NS	**Key confounders:** Sex, age, SES, physical activity, smoking, alcohol pattern (for alcohol intake), alcohol intake (for alcohol pattern) **Other factors considered:** total energy intake, anthropometry, hypertension, diabetes **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality • Exposure data measurement tool not validated • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Sluik, 2014[50] Prospective Cohort Study European Prospective Investigation into Cancer and Nutrition (EPIC) Denmark, Germany, Italy, Netherlands, Spain, Sweden N= 258,911 **Participants**: ~52y (35-70y), 60% female, BMI ~26 kg/m^2, 28% current smokers	**Baseline**: 1992-2000 **Follow-up**: ~9.9y **Average intake, FFQ**: • 0 g/d (does not distinguish between never and former) • **>0-6 g/d (REF)** • >6-12 g/d • >12-24 g/d • >24-60 g/d • >60 g/d	• >0-6 g/d: REF • **>6-12 g/d: 0.80 (0.75, 0.85)** • **>12-24 g/d: 0.79 (0.75, 0.84)** • **>24-60 g/d: 0.87 (0.82, 0.93)** • **>60 g/d: 1.13 (1.04, 1.23)**	**Key confounders:** Sex, age, race/ethnicity, SES (education), eating pattern or diet quality, physical activity, smoking **Other factors considered:** N/A **Other:** study center, self-reported myocardial infarction, stroke or cancer at baseline,	• **Key confounders NOT accounted for**: alcohol pattern (for intake exposure) • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up may differ among participants (outcome assessment time NR) • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Smyth, 2015[51] Prospective Cohort Study Prospective Urban Rural Epidemiology (PURE) study 12 Countries: Sweden, Canada, Argentina, Brazil, Chile, Poland, South Africa, Turkey, China, Colombia, India, Zimbabwe N= 114,970 **Participants**: ~50y (35-70y), 58% female; Current drinkers (31%): ~50y, 34% female, BMI ~25 kg/m^2	**Baseline**: NR **Follow-up**: 2014 (~4.3y) *Alcohol History*: • ***Never drinker (REF):*** self-reported abstinence • Former drinker: no alcohol for ≥1y • Current drinker: within the past year *Intake level, current drinkers*: • Low intake: ≤7 drinks/wk • Moderate intake: 7-14 drinks/wk for women; 7-21 drinks/wk for men • High intake: >14 drinks/wk for women; >21 drinks/wk for men *Heavy episodic drinking, current drinkers*: • No • Yes: >5 drinks in 1 episode at least 1/mo	• Never drinker: REF • **Former drinker: 1.56 (1.27, 1.92)** • Current drinker: 1.00 (0.87, 1.14) • Low intake: 0.97 (0.84, 1.13) • Moderate intake: 0.97 (0.79, 1.18) • **High intake: 1.31, (1.04, 1.66)** • Not Heavy episodic drinkers: 0.94 (0.80, 1.10) • **Heavy episodic drinkers: 1.54 (1.27, 1.87)**	**Key confounders:** Sex, age, race/ethnicity, SES (education, wealth index), eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** anthropometry, hypertension, diabetes, medications, **Other:** jaundice or hepatitis, community-level clustering included as a random effect	• Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Soedamah-Mutha, 2013[52] Prospective Cohort Study Health Surveys for England (HSE), Scottish Health Surveys (SHS) England and Scotland N= 17,410 **Participants**: ~55y (40-95y), 57% female; excluded those diagnosed with DM, prevalent CVD, those who stopped drinking due to health conditions, and those with missing values for mortality and social class	**Baseline**: HSE: 1997, 1998; SHS: 1998, 2003 **Follow-up**: 2008 **Average intake:** • None: during past 12 mo (combines never/former drinkers therefore data not extracted) • ***Moderate (REF):*** >0 to 21 weekly units for men; >0 to 14 weekly units for women • Moderately high: >21 to 35 weekly units for men; >14 to 21 weekly units for women • High: >35 weekly units for men and >21 weekly units for women 1 unit = 8g ethanol = 125 ml glass of wine = ½ pint regular strength beer	• Moderate: REF • Moderately high: 1.08 (0.93, 1.26) • **High: 1.26 (1.08, 1.48), P=0.004**	**Key confounders:** sex, age, race/ethnicity, SES, physical activity, smoking **Other factors considered:** anthropometry (BMI) **Other:** marital status, survey, longstanding illness, changes in alcohol consumption at baseline	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Selection into the analysis was based on characteristics potentially associated with the exposure and outcome • Exposure data measurement tool not validated • Exposure data only measured once • Length of follow-up differs among participants • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Stringhini, 2011[53] Prospective Cohort Study, Whitehall II and GAZEL United Kingdom and France N=9,771 (Whitehall II) and 17,760 (GAZEL) **Participants**: Whitehall II: 35-55y (~44y), 32% female; excluded those with missing data on health behaviors at baseline and those not followed-up for mortality GAZEL: 35-50y (~43y), 26% female; excluded those with missing data and those that diet before start of follow-up	**Baseline**: Whitehall II: Phase 1, 1985-1988; GAZEL: 1990-1995 Follow-up: Whitehall II: Phase 3 (1991-93), Phase 5 (1997-99), and Phase 7 (2002-04); GAZEL: 1992, 1998, 2004 **Follow-up (outcome)**: Whitehall II: 2009 (~19.5y); GAZEL: 2009 (~16.5y) **Average intake**: • Abstainers: 0 units/wk (likely combines never + former) • ***Moderate drinkers (REF):*** 1-21 units/wk (men) or 1-14 units/wk (women) • Heavy drinkers: >21 units/wk (men) or >14 units/wk (women)	Whitehall II Moderate (REF) **Heavy: 1.25 (1.02, 1.52)** GAZEL Moderate (REF) Heavy: 1.16 (0.99, 1.36) P-interaction between cohort: NS	**Key confounders:** Sex, age **Other factors considered:** N/A **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, SES, eating pattern or diet quality, physical activity, smoking, alcohol pattern • Exposure data measurement tool not validated • Excluded participants had higher mortality rate and lower SES • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Syden, 2017[54] Prospective Cohort Study Stockholm Public Health Survey Sweden N= 21,064 **Participants**: 46y (25-74y), 55% female, excluded those with diabetes, angina pectoris, infarct, heart failure or stroke at baseline, or missing data	**Baseline**: 2002 **Follow-up**: 2007 (5y) **Average intake:** • Abstainers (likely never+former) • Light drinkers (0–84 g 100% alcohol/wk) • ***Moderate drinkers (REF):*** men: >84–252, women: 84–168 g 100% alcohol/wk • Heavy drinkers (men: 252, women: >168 g 100% alcohol/wk) **Pattern of intake:** Heavy episodic drinking (HED) (minimum 120g 100% alcohol (e.g. two bottles of wine/6 cans of strong beer/a half bottle of spirits) • Abstainers • ***No HED, REF*** • HED 1–6 times/y • HED 1–3 times/mo • HED>once/wk **Average + Pattern** • Abstainers • Light drinkers, no HED • Light drinkers, HED • ***Moderate drinkers, no HED, REF*** • Moderate drinkers, HED 1–6 times/y • Moderate drinkers, HED>monthly • Heavy drinkers, no HED • Heavy drinkers, HED 1–6 times/y • Heavy drinkers, HED 1–3 times/mo • Heavy drinkers, HED>once/wk	Average intake: • Light consumers: 1.18 (0.85, 1.63) • Moderate consumers: 1.00 REF • **Heavy consumers: 2.21 (1.50, 3.26)** Pattern: Heavy episodic drinking (HED) • No HED: 1.00 REF • **HED 1–6 times/y: 1.63 (1.09, 2.44)** • HED 1–3 times/mo: 1.19 (0.70, 2.04) • **HED >once/wk: 3.14 (2.03, 4.85)** Average + Pattern • Light drinkers, no HED: 1.43 (0.94, 2.18) • **Light drinkers, HED: 2.03 (1.16, 3.55)** • Moderate drinkers, no HED: 1.00 REF • **Moderate drinkers, HED 1–6 times/y: 1.85 (1.01, 3.39)** • **Moderate drinkers, HED>mo: 2.21 (1.22, 4.01)** • **Heavy drinkers, no HED: 2.30 (1.23, 4.29)** • **Heavy drinkers, HED 1–6 times/y: 3.93 (1.90, 8.13)** • **Heavy drinkers, HED 1–3 times/mo: 2.48 (1.05, 5.82)** • **Heavy drinkers, HED>once a week 3.80 (1.97, 7.35)** **Findings stratified by socioeconomic position differences provided in paper.**	**Key confounders:** Sex, age, **Other factors considered:** None **Other:** None	• **Key confounders NOT accounted for**: race/ethnicity, SES, eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) • Exposure data measurement tool not validated • Exposure data only measured once • Abstainers likely include both never and former drinkers • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Tevik, 2019[55] Prospective Cohort Study Nord-Trøndelag Health Study (HUNT) Norway N=7,262 **Participants:** 74y (all ≥65y); 53% female; excluded participants with missing data on drinking frequency	**Baseline:** 2006-2008 **Follow up:** 2013 **Average intake:** • Never • Former (not in past year) • ***Few times/year (REF)*** • 1x / month • 2-3 days/month • 1 day/wk • 2-3 day/wk • 4-7 day/wk	Logistic regression, OR (95% CI) • Never: NS • Former: NS • Few times/year (REF) • 1x/mo: NS • 2-3 d/mo: NS • 1 d/wk: NS • 2-3 d/wk: NS • 4-7 d/wk: NS Stratifying by age group (65-74y and 75y+) did not change results **Sensitivity analyses excluding never and former drinkers did not change findings**	**Key confounders:** Sex, age, SES (education, marital status) **Other factors considered:** Age distribution of the study sample, hypertension, blood pressure, diabetes, lipids, overall health status, physical health, mental health **Other:** Urban/rural living area	• **Key confounders NOT accounted for**: Race/ethnicity, eating pattern or diet quality, physical activity, smoking, alcohol pattern (for intake exposure) • Older cohort: Potential survival bias • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

van den Brandt, 2020[56] Prospective Cohort Study Netherlands Cohort Study (NLCS) The Netherlands N=5,479 **Participants**: 68-70y, 53% female, Selected participants were all born 1916-1917; excluded participants with missing data on alcohol intake and covariates	**Baseline**: 1986 **Follow-up**: 2006-2007 **Average intake** • Continuous (per 10 g/d) • Categorical • ***Abstainers (REF)*** • Ex-drinker (0 g/d) • >0-<5 g/d • 5-<10 g/d • 10-<15 g/d • 15-<30 g/d • ≥30 g/d **Pattern of alcohol drinking** • ***Only at parties (REF)*** • Weekend and parties • Throughout the week **Binge drinking in last 6 months** • ***No (REF)*** • Yes (>6 drinks/occasion) **Frequency of ≥7 drinks/occasion in last 6 months** • ***0 times (REF)*** • 1-<2 times • 2-<3 times • 3-<5 times • ≥5 times	**RR (95% CI) for reaching longevity until age 90** **Overall** *Average intake* Abstainers (REF) Ex-drinker: 0.84 (0.48, 1.47) **>0-<5 g/d: 1.19 (1.07, 1.33)** **5-<10 g/d: 1.41 (1.21, 1.63)** **10-<15 g/d: 1.30 (1.10, 1.55)** **15-<30 g/d: 1.29 (1.10, 1.52)** **≥30 g/d: 1.31 (1.06, 1.63)** **P-trend (excluding ex-drinkers): 0.014** *Per 10 g/d (excluding ex-drinkers)* **1.05 (1.01, 1.09)** P-interaction: 0.168 **Stable Subgroup** (reported same intake 5y before baseline) *Alcohol intake* Abstainers (REF) **>0-<5 g/d: 1.25 (1.09, 1.43)** **5-<10 g/d: 1.42 (1.18, 1.70)** **10-<15 g/d: 1.30 (1.05, 1.60)** **15-<30 g/d: 1.31 (1.08, 1.59)** **≥30 g/d: 1.36 (1.05, 1.76)** **P-trend (excluding ex-drinkers): 0.024** *Per 10 g/d (excluding ex-drinkers)* 1.05 (1.00, 1.11) P-interaction: 0.468 **Men** *Average intake* Abstainers (REF) Ex-drinker: 1.49 (0.69, 3.23) **>0-<5 g/d: 1.39 (1.01, 1.90)** **5-<10 g/d: 1.81 (1.30, 2.53)**	**Key confounders:** Sex, age, SES (education), physical activity, smoking, alcohol pattern (for intake exposure), alcohol intake (for pattern exposure) **Other factors considered:** total energy intake, age distribution of the study sample, anthropometry, hypertension, diabetes, beverage type (e.g., beer, wine, spirits) **Other:** myocardial infarction, angina pectoris, stroke, cancer (excluding skin cancer)	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality • Exposure data only measured once • No preregistered data analysis plan

10-<15 g/d: 1.37 (0.95, 1.97)
15-<30 g/d: 1.43 (1.02, 1.99)
≥30 g/d: 1.64 (1.15, 2.34)
P-trend (excluding ex-drinkers): 0.100

Per 10 g/d (excluding ex-drinkers)
1.04 (0.98, 1.10)

Pattern of alcohol drinking
Only at parties (REF)
Weekend and parties: NS
Throughout the week: NS
P-trend: NS
P-interaction with alcohol: NS

Binge drinking in last 6 months
No (REF)
Yes: NS
P-interaction with alcohol: NS

Frequency of ≥7 drinks/occasion in last 6 months
0 times (REF)
1-<2 times: NS
2-<3 times: NS
3-<5 times: NS
≥5 times: NS
P-trend: NS
P-interaction with alcohol: NS

Women
Average intake
Abstainers (REF)
Ex-drinker: 0.62 (0.27, 1.38)
>0-<5 g/d: 1.17 (1.03, 1.32)
5-<10 g/d: 1.28 (1.08, 1.52)
10-<15 g/d: 1.38 (1.13, 1.68)
15-<30 g/d: 1.31 (1.08, 1.60)
≥30 g/d: 0.99 (0.69, 1.44)
P-trend (excluding ex-drinkers): 0.078

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
		Per 10 g/d (excluding ex-drinkers) 1.05 (0.99, 1.11) *Pattern of alcohol drinking* Only at parties (REF) Weekend and parties: NS Throughout the week: NS P-trend: NS P-interaction with alcohol: NS *Binge drinking in last 6 months* No (REF) Yes: NS P-interaction with alcohol: NS *Frequency of ≥7 drinks/occasion in last 6 months* 0 times (REF) 1-<2 times: NS 2-<3 times: NS 3-<5 times: NS ≥5 times: NS P-trend: NS P-interaction with alcohol: NS **Sex-specific data on beer, wine, and liquor available in paper**		

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Van Hedel, 2018[57] Prospective Cohort Study Dutch GLOBE Study The Netherlands N=13,034 **Participants**: 25-74y, 53% female; excluded participants with chronic obstructive pulmonary disease, heart disease, stroke, renal disease, diabetes, or cancer	**Baseline**: 1991 **Follow-up**: 2014 (23y) **Average intake:** • No consumption (likely combines never + former) • ***Light consumption (1-14 drinks/wk for men, 1-7 drinks/wk for women), REF*** • Moderate consumption • (15-21 drinks/wk for men, 8-14 drinks/wk for women) • Heavy consumption (22+ drinks/wk for men, 15+ drinks/wk for women)	• Light = REF • Moderate 1.12 (0.94, 1.32) • **Heavy: 1.71 (1.48, 1.98)**	**Key confounders:** Sex, age, SES (education) **Other factors considered:** None **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, eating pattern or diet quality, physical activity, smoking, alcohol intake • Exposure data measurement tool likely not validated • Exposure data only measured once • Not clear if the “no consumption” group included both never and former drinkers • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Warren Andersen, 2016[58] Prospective Cohort Study, Southern Community Cohort Study (SCCS) United States N=79,101 **Participants:** 51y (40-79y), 57% female; eligible participants spoke English and were not under treatment for cancer within the prior year; excluded those with <1 year of follow-up time or missing data for smoking status, alcohol intake, physical activity, and sedentary behavior	**Baseline**: 2002-2009 **Follow-up**: 2011 **Average intake:** • Nondrinker (never+former) • ***Moderate (REF):*** >0 but ≤1 drink/d for women or ≤2 for men • Heavy	<u>All Participants</u> • Moderate (n=28,155, REF) • **Heavy (n=14075): 1.21 (1.13, 1.29)** <u>African American Men</u> • Moderate (n=941, REF) • **Heavy (n=875): 1.18 (1.07, 1.30)** <u>White Men</u> • Moderate (n=341, REF) • **Heavy (n=252): 1.35 (1.14, 1.59)** <u>African American Women</u> • Moderate (n=541, REF) • **Heavy (n=322): 1.26 (1.09, 1.45)** <u>White Women</u> • Moderate (n=268, REF) • Heavy (n=89): 1.26 (0.99, 1.61)	**Key confounders:** Sex, age, race/ethnicity, SES (education, income, marital status, neighborhood deprivation), eating pattern or diet quality (HEI), physical activity, smoking **Other factors considered:** anthropometry **Other:** Enrollment source, sedentary time	• **Key confounders NOT accounted for**: alcohol pattern • Exposure data only measured once • Length of follow-up differs among participants • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Wood, 2018[59] Prospective Cohort Study, Emerging Risk Factors Collaboration (ERFC), EPIC-CVD, UK Biobank 19 "high-income" countries N=599,912 **Participants**: 56y (SD: 9), 21% female, included data from current drinkers in 83 prospective studies in 19 different high-income countries; excluded those with CVD at baseline	**Baseline**: 1964-2008 (ERFC), 1990-2002 (EPIC), 2006-10 (UK Biobank) **Follow-up**: 2013, 2009, 2016 (5.4million person years) **Average intake:** • ***>0–≤25 g/wk alcohol, REF*** • >25–≤50 g/wk alcohol • >50–≤75 g/wk alcohol • >75–≤100 g/wk alcohol • >100–≤150 g/wk alcohol • >150–≤250 g/wk alcohol • >250–≤350 g/wk alcohol • >350 g/wk alcohol	Higher alcohol intake was associated with higher risk of ACM, with the lowest risk for <100 g/wk, data not reported (Figure Only) Associations were similar for men and women	**Key confounders:** Sex, age, smoking **Other factors considered:** diabetes **Other:** N/A	• **Key confounders NOT accounted for**: race/ethnicity, SES, eating pattern or diet quality, physical activity, alcohol pattern • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Articles	Time and Exposure Groups	Results *(all results are HR (95% CI) unless otherwise noted)*	Confounders accounted for	Limitations
Xi, 2017[60] Prospective Cohort Study National Health Interview Surveys United States N=34,754 **Participants**: >18y (40% 18-39y, 37% 40-59y, 22% >60y), 51% female; excluded those with missing data, who were pregnant, or who died in the first 2 years of follow up	**Baseline**: 1997-2009 **Follow-up**: 2011 (8.2y) **Average intake: frequency + pattern** • ***Lifetime abstainers (REF):*** <12 drinks in one's lifetime • Lifetime infrequent drinkers (>12 lifetime drinks, <12 drinks in last year) • Former-drinkers (<12 drinks in last year) • Current light drinkers (<3 drinks wk) • Current moderate drinkers (>3 and <14 for men and <7 for women drinks/wk) • Current heavy drinkers (>14 drinks/wk for men or >7 for women) Binge-drinking: 5+ drinks/d	<u>Average intake</u> • Lifetime abstainers, REF • Lifetime infrequent drinkers: 1.02 (0.98, 1.06) • Former-drinkers: 1.04 (0.99, 1.09) • **Current light drinkers: 0.80 (0.77, 0.93)** • **Current moderate drinkers: 0.81 (0.77, 0.85)** • **Current heavy drinkers: 1.13 (1.05, 1.21)** <u>Binge-Drinking Status:</u> • Lifetime abstainer, REF • **Drinker without binge-drinking: 0.81 (0.78, 0.85)** • **Drinker with binge-drinking <1/mo: 0.87 (0.80, 0.95)** • Drinker with binge-drinking <1d/wk: 0.94 (0.82, 1.07) • **Drinker with binge-drinking >1d/wk: 1.16 (1.07, 1.27)**	**Key confounders:** Sex, age, race/ethnicity, SES (education, marital status), eating pattern or diet quality, physical activity, smoking **Other factors considered:** anthropometry, hypertension, heart disease, stroke, cancer, diabetes **Other:** N/A	• **Key confounders NOT accounted for**: eating pattern or diet quality, alcohol intake • Exposure data measurement tool not validated • Exposure data only measured once • No information on non-completers • No preregistered data analysis plan

Table 2: Risk of bias for observational studies examining alcohol consumption and all-cause mortality[vi,vii,viii]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Almeida, 2017,[1] MR	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Bellavia, 2014,[2] PCS	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate
Bergmann, 2013,[3] PCS	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate
Bobak, 2016,[4] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Britton, 2010,[5] PCS	Serious	Low	Moderate	Low	Moderate	Low	Moderate
Britton, 2016,[6] PCS	Serious	Low	Moderate	Moderate	Low	Low	Moderate
Degerud, 2020,[7] PCS	Serious	Moderate	Moderate	Moderate	Low	Low	Moderate
Evans-Polce, 2016,[8] PCS	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Ferrari, 2014,[9] PCS	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate
Gea, 2014,[10] PCS	Serious	Moderate	Low	Moderate	Low	Low	Moderate
Goulden, 2016,[11] PCS	Serious	Moderate	Moderate	Low	Low	Low	Moderate
Graff-Iversen, 2013,[12] PCS	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Hartz, 2018,[13] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Holahan, 2010,[14] PCS	Serious	Low	Moderate	Moderate	Low	Low	Moderate
Holahan, 2015,[15] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Horvat, 2018,[16] RCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Jackson, 2015,[17] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Jayasekara,[18] 2015	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Jung, 2012,[19] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Kabat, 2015,[20] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Kerr, 2011,[21] PCS	Serious	Moderate	Low	Moderate	No information	Low	Serious
Keyes, 2019,[22] PCS	Serious	Moderate	Moderate	Low	Low	Low	Moderate
Knott, 2015,[23] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Kunzmann, 2018,[24] PCS	Serious	Serious	Low	Moderate	Moderate	Low	Moderate

[vi] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

[vii] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

[viii] Abbreviations: MR, Mendelian randomization; PCS, prospective cohort study; RCS, retrospective cohort study

Lantz, 2010,[25] PCS	Serious	Low	Serious	Low	Moderate	Low	Moderate
Li, 2018,[26] PCS	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate
Licaj, 2016,[27] PCS	Serious	Low	Moderate	Low	Moderate	Low	Moderate
Lindschou, 2011,[28] PCS	Serious	Serious	Low	Moderate	Moderate	Low	Moderate
Luksiene, 2017,[29] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Lundin, 2015a,[30] PCS	Serious	Low	Moderate	Moderate	Low	Low	Moderate
Lundin, 2015b,[31] PCS	Serious	Low	Moderate	Moderate	Low	Low	Moderate
McCullough, 2011,[32] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Midlov, 2016,[33] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Muller, 2016,[34] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Ortola, 2019,[35] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Pan, 2019,[36] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Perreault, 2017,[37] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Plunk, 2014,[38] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Powell, 2020,[39] PCS	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Rhee, 2012,[40] PCS	Serious	Serious	Serious	Moderate	Moderate	Low	Moderate
Ricci, 2020,[41] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Rosella, 2019,[42] PCS	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Rostron, 2012,[43] PCS	Serious	Low	Moderate	Moderate	Moderate	Low	Moderate
Rundberg, 2014,[44] PCS	Serious	Serious	Moderate	Moderate	Serious	Low	Moderate
Schoenborn, 2014,[45] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Schutte, 2020,[46] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Shuval, 2012,[47] PCS	Serious	Moderate	Serious	Moderate	Moderate	Low	Moderate
Simpson, 2016,[48] PCS	Serious	Moderate	Low	Moderate	Low	Low	Moderate
Skov-Ettrup, 2011,[49] PCS	Serious	Moderate	Moderate	Low	Moderate	Low	Moderate
Sluik, 2014,[50] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Smyth, 2015,[51] PCS	Serious	Moderate	Moderate	Moderate	Low	Low	Moderate
Soedamah-Muthu, 2013,[52] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Stringhini, 2011,[53] PCS	Serious	Low	Moderate	Low	Moderate	Low	Moderate
Syden, 2017,[54] PCS	Serious	Serious	Moderate	Moderate	Moderate	Low	Moderate
Tevik, 2019,[55] PCS	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate
van den Brandt, 2020,[56] PCS	Serious	Low	Low	Moderate	Moderate	Low	Moderate
van Hedel, 2018,[57] PCS	Serious	Serious	Serious	Serious	Low	Low	Moderate
Warren Andersen, 2016,[58] PCS	Serious	Moderate	Low	Moderate	Low	Low	Moderate
Wood, 2018,[59] PCS	Serious	Serious	Low	Serious	Serious	Low	Moderate
Xi, 2017,[60] PCS	Serious	Moderate	Moderate	Serious	Moderate	Low	Moderate

METHODOLOGY

The NESR team used its rigorous, protocol-driven methodology to support the 2020 Dietary Guidelines Advisory Committee in conducting this systematic review.

NESR's systematic review methodology involves:

- Developing a protocol,
- Searching for and selecting studies,
- Extracting data from and assessing the risk of bias of each included study,
- Synthesizing the evidence,
- Developing conclusion statements,
- Grading the evidence underlying the conclusion statements, and
- Recommending future research.

A detailed description of the methodology used in conducting this systematic review is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews, and can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part C: Methodology.[ix] This systematic review was peer reviewed by Federal scientists, and information about the peer review process can also be found in the Committee's Report, Part C. Methodology. Additional information about this systematic review, including a description of and rationale for any modifications made to the protocol can be found in the in the 2020 Dietary Guidelines Advisory Committee Report, Chapter 11. Alcoholic Beverages.

Below are details of the final protocol for the systematic review described herein, including the:

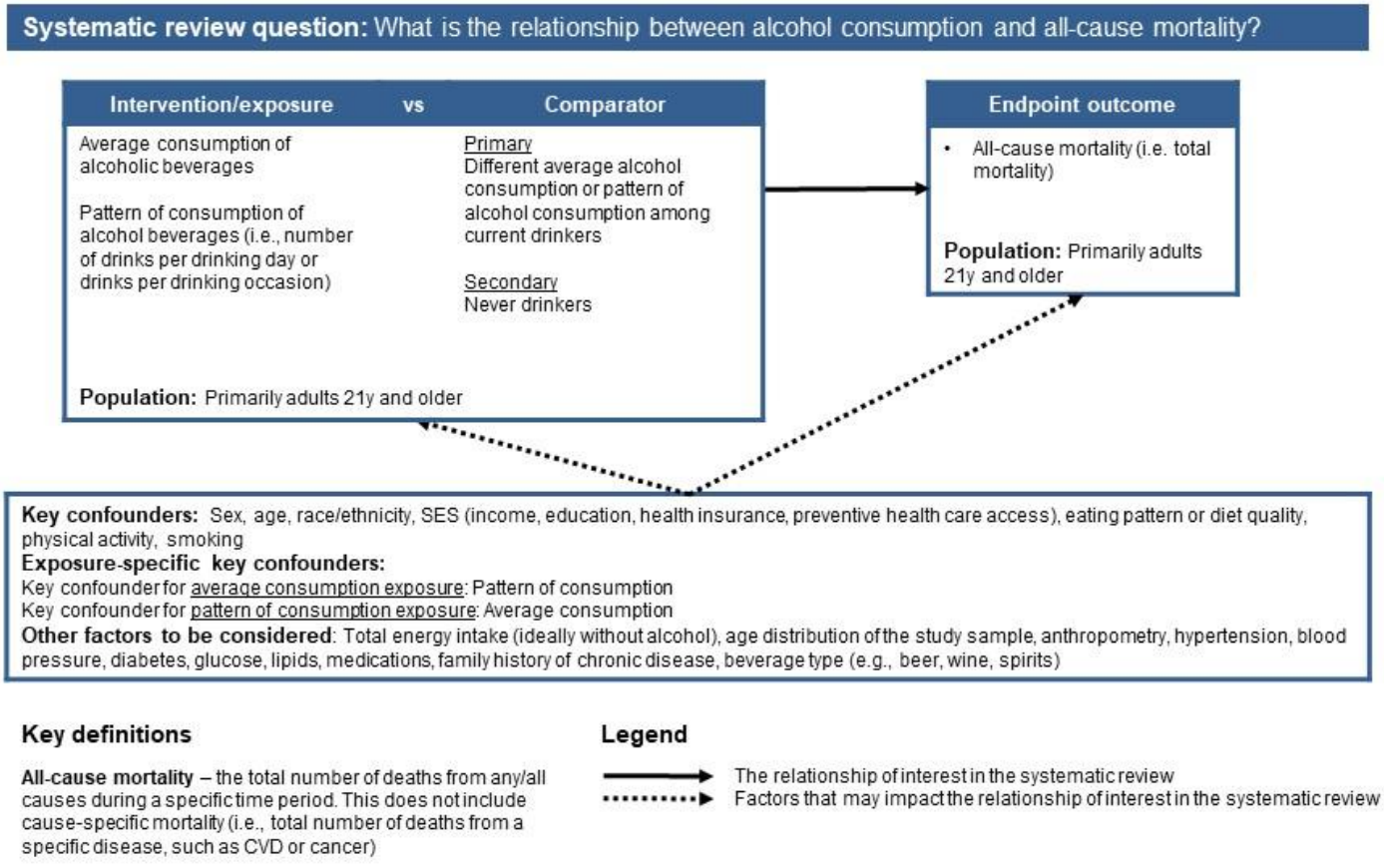
- Analytic framework
- Literature search and screening plan
- Literature search and screening results

[ix] Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

ANALYTIC FRAMEWORK

The analytic framework (**Figure 1**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework were defined and operationalized for the review.

Figure 1: Analytic framework



LITERATURE SEARCH AND SCREENING PLAN

Inclusion and exclusion criteria

Table 3 provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search were included in or excluded from the systematic review.

Table 3: Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Mendelian randomization studies • Non-randomized controlled trials including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies	• Uncontrolled trials • Case-control studies • Cross-sectional studies • Uncontrolled before-and-after studies • Narrative reviews • Systematic reviews • Meta-analyses
Sample size	• Observational studies enrolling >1,000 participants	• Observational studies enrolling <1,000 participants
Intervention/ exposure	Average consumption of alcoholic beverages Per occasion consumption of alcohol beverages (i.e., number of drinks per drinking day or drinks per drinking occasion) • Information on type of beverage (e.g., beer, wine, spirits) will be collected if available	• Data on 'non-drinker' groups where never and former drinkers are combined
Comparator	<u>Primary</u> • Comparisons across different average alcohol consumption or pattern of alcohol consumption among current drinkers <u>Secondary</u> • Comparisons between never drinkers and current drinkers	No comparator • Comparisons with never and former drinkers as a combined 'non-drinker' group
Outcomes	• All-cause mortality (i.e. total mortality): the total number of deaths from all causes during a specific time period. • (Ideally stratified by sex)	• Studies that only report cause-specific mortality (total number of deaths from a specific disease, such as cardiovascular disease or cancer)

Category	Inclusion Criteria	Exclusion Criteria
Date of publication	• January 2010 – March 2020	• Articles published prior to January 2010
Publication status	• Articles published in peer-reviewed journals	• Articles not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, pre-prints, and conference proceedings
Language of publication	• Articles published in English	• Articles published in languages other than English
Country[x]	• Studies conducted in Very High or High Human Development Countries	• Studies conducted in Medium or lower Human Development Countries
Study participants	• Human participants • Males • Females	• Animal subjects • Hospitalized samples
Age of study participants	• Primarily adults 21y and older • Studies that enroll *some* participants under 21 years old	• Studies that *exclusively* enroll participants under 21 years old
Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity • Studies that enroll *some* participants diagnosed with a disease	• Studies that *exclusively* enroll participants diagnosed with a disease or hospitalized with an illness or injury. (For this criterion, studies that exclusively enroll subjects with obesity will not be excluded)

[x] The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 -world- country-and-lending-groups).

Electronic databases and search terms

Listed below are the databases searched to identify all potentially relevant articles that have been published to address the update to the existing systematic review.

PubMed

- Provider: U.S. National Library of Medicine
- Date(s) Searched: March 11, 2020
- Date range searched: January 1, 2000-March 11, 2020
- Search Terms:

#1 - “Alcohol-Induced Disorders"[Mesh] OR alcohol intake*[tiab] OR alcohol consum*[tiab] OR "Alcohol Drinking"[Mesh] OR alcohol drink*[tiab] OR "Alcoholic Beverages"[Mesh] OR alcoholic beverage*[tiab] OR beer*[tiab] OR wine*[tiab] OR liquor[tiab] OR liqueur*[tiab] OR spirits[tiab] OR "Ethanol"[Mesh] OR ethanol[tiab]

#2 - "Mortality"[Mesh] OR "mortality" [Subheading] OR mortality[tiab]

#3 - (#1 AND #2) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti]) Filters: Publication date from 2000/01/01 to 2020/03/11; English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) Searched: March 11, 2020
- Date range searched: January 1, 2000-March 11, 2020
- Search Terms:

#1 - [mh "Alcohol-Induced Disorders"] OR [mh "Alcohol Drinking"] OR [mh "Alcoholic Beverages"] OR [mh "Ethanol"]

#2 - ("alcohol intake*" OR "alcohol consum*" OR "alcohol drink*" OR "alcoholic beverage*" OR beer* OR wine* OR liquor OR liqueur* OR spirits OR ethanol):ti,ab,kw

#3 - #1 OR #2

#4 - ([mh "Mortality"] OR [mh /MO] OR mortality):ti,ab,kw"

#5 - #3 AND #4

#6 - #3 AND #4" with Publication Year from 2000 to 2020, in Trials (Word variations have been searched)

Embase

- Provider: Elsevier
- Date(s) Searched: March 11, 2020
- Date range searched: January 1, 2000-March 11, 2020
- Search Terms**:**

#1 - 'alcoholism'/exp OR 'drinking behavior'/de OR 'alcoholic beverage'/exp OR 'alcohol'/de

#2 - 'alcohol intake*':ab,ti OR 'alcohol consum*':ab,ti OR 'alcohol drink*':ab,ti OR 'alcoholic beverage*':ab,ti OR beer*:ab,ti OR wine*:ab,ti OR liquor:ab,ti OR liqueur*:ab,ti OR spirits:ab,ti

#3 - #1 OR #2

#4 - 'mortality'/exp OR mortality:ab,ti

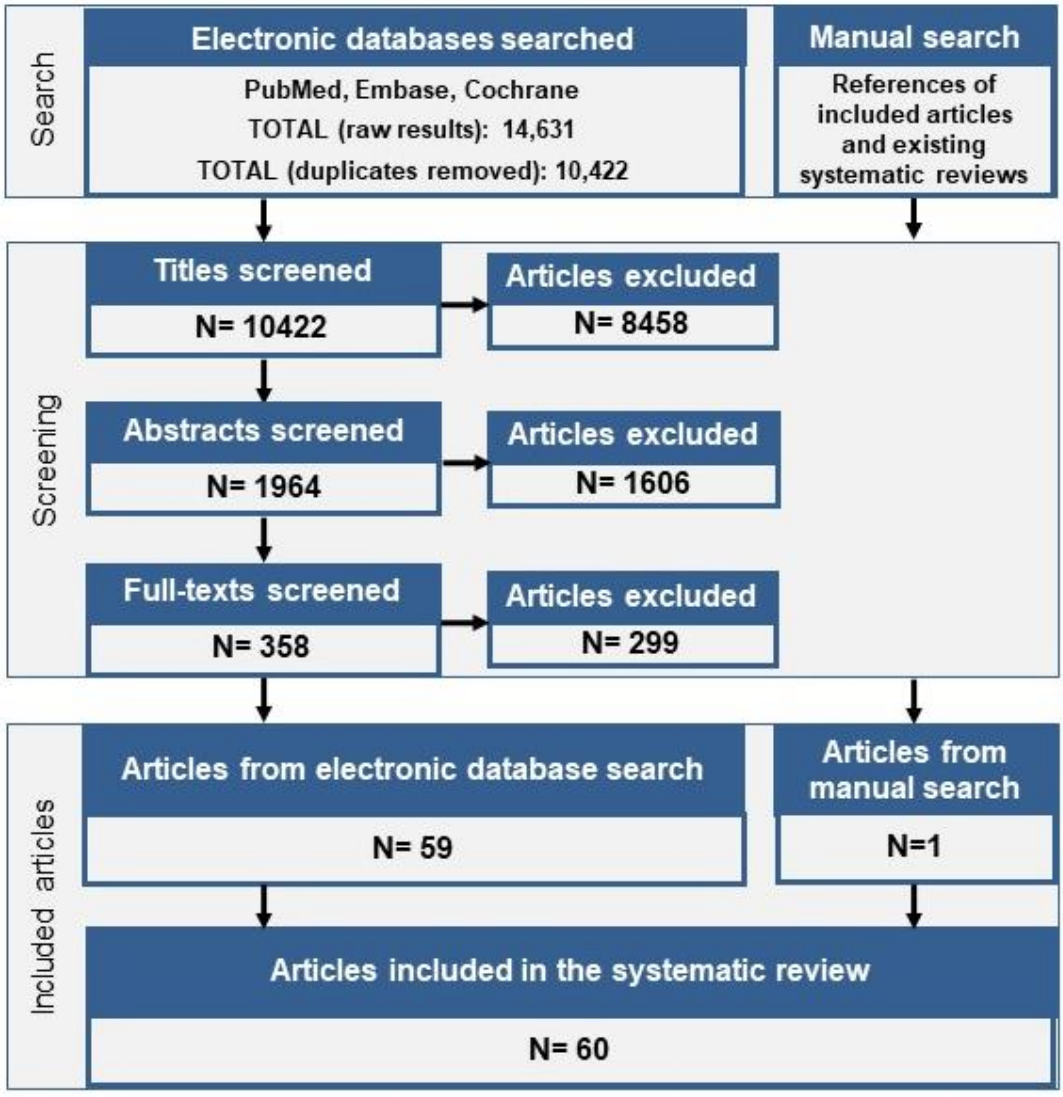
#5 - #3 AND #4

#6 - #3 AND #4 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [2000-2020]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

LITERATURE SEARCH AND SCREENING RESULTS

The flow chart (**Figure 2**) below illustrates the literature search and screening results for articles examining the systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. Refer to **Table 4** for the rationale for exclusion for each excluded full-text article. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

Figure 2: Flow chart of literature search and screening results



Excluded articles

The table below lists the articles excluded after full-text screening, and includes categories of inclusion and exclusion criteria (see **Table 3**) that studies were excluded. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons for exclusion. Information about articles excluded after title and abstract screening is available upon request.

Table 4: Articles excluded after full text screening with rationale for exclusion

	Citation	Rationale
1	Aburto JM, van Raalte A. Lifespan dispersion in times of life expectancy fluctuation: the case of Central and Eastern Europe. *Demography*. 2018. 55(6):2071-2096. doi:10.1007/s13524-018-0729-9.	Study Design; Intervention/Exposure
2	Agahi N, Kelfve S, Lennartsson C, Kareholt I. Alcohol consumption in very old age and its association with survival: A matter of health and physical function. *Drug Alcohol Depend*. 2016. 159:240-5. doi:10.1016/j.drugalcdep.2015.12.022.	Sample size
3	Akbaraly TN, Ferrie JE, Berr C, Brunner EJ, Head J, Marmot MG, Singh-Manoux A, Ritchie K, Shipley, MJ, Kivimaki, M. Alternative Healthy Eating Index and mortality over 18 y of follow-up: results from the Whitehall II cohort. *Am J Clin Nutr*. 2011. 94(1):247-53. doi:10.3945/ajcn.111.013128.	Comparator
4	AlGhatrif M, Markides KS, Kuo YF, Ray LA, Moore AA. The effect of prevalent cardiovascular conditions on the association between alcohol consumption and mortality among older Mexican American men. *Ethn Dis*. 2013. 23(2):168-74.	Sample size
5	Arndt V, Rothenbacher D, Krauledat R, Daniel U, Brenner H. Age, alcohol consumption, and all-cause mortality. *Ann Epidemiol*. 2004. 14(10):750-3. doi:10.1016/j.annepidem.2004.01.004.	Publication Date
6	Baer HJ, Glynn RJ, Hu FB, Hankinson SE, Willett WC, Colditz GA, Stampfer M, Rosner B. Risk factors for mortality in the nurses' health study: a competing risks analysis. *Am J Epidemiol*. 2011. 173(3):319-29. doi:10.1093/aje/kwq368.	Comparator
7	Baglietto L, English DR, Hopper JL, Powles J, Giles GG. Average volume of alcohol consumed, type of beverage, drinking pattern and the risk of death from all causes. *Alcohol Alcohol*. 2006. 41(6):664-71. doi:10.1093/alcalc/agl087.	Publication Date
8	Bahat G, Tufan F, Bahat Z, Tufan A , Aydin Y, Akpinar TS, Erten N, Karan MA. Observational cohort study on correlates of mortality in older community-dwelling outpatients: The value of functional assessment. *Geriatr Gerontol Int*. 2015. 15(11):1219-26. doi:10.1111/ggi.12422.	Intervention/Exposure
9	Bartak M. Alcohol Consumption and Cause-Specific Mortality in Russia: A View From the Czech Republic. *J Stud Alcohol Drugs*. 2019. 80(5):503-504.	Study Design; Publication Status
10	Batty GD, Lewars H, Emslie C, Gale CR, Hunt K. Internationally recognized guidelines for 'sensible' alcohol consumption: is exceeding them actually detrimental to health and social circumstances? Evidence from a population-based cohort study. *J Public Health (Oxf)*. 2009. 31(3):360-5. doi:10.1093/pubmed/fdp063.	Publication Date
11	Bazzano LA, Gu D, Reynolds K, Chen J, Wu X, Chen CS, Duan X, Chen J, He J. Alcohol consumption and risk of coronary heart disease among Chinese men. *Int J Cardiol*. 2009. 135(1):78-85. doi:10.1016/j.ijcard.2008.03.038.	Outcome
12	Behrens G, Leitzmann MF, Sandin S, Lof M, Heid IM, Adami HO, Weiderpass E. The association between alcohol consumption and mortality: the Swedish women's lifestyle and health study. *Eur J Epidemiol*. 2011. 26(2):81-90. doi:10.1007/s10654-011-9545-x.	Comparator
13	Bellavia A, Tektonidis TG, Orsini N, Wolk A, Larsson SC. Quantifying the benefits of Mediterranean diet in terms of survival. *Eur J Epidemiol*. 2016. 31(5):527-30. doi:10.1007/s10654-016-0127-9.	Intervention/Exposure
14	Bobak M, Murphy M, Rose R, Marmot M. Determinants of adult mortality in Russia: estimates from sibling data. *Epidemiology*. 2003. 14(5):603-11. doi:10.1097/01.ede.0000082000.75818.4d.	Publication Date

	Citation	Rationale
15	Bondonno NP, Lewis JR, Blekkenhorst LC, Bondonno CP, Shin JH, Croft KD, Woodman RJ, Wong G, Lim WH, Gopinath B, Flood VM, Russell J, Mitchell P, Hodgson JM. Association of flavonoids and flavonoid-rich foods with all-cause mortality: The Blue Mountains Eye Study. *Clin Nutr*. 2020. 39(1):141-150. doi:10.1016/j.clnu.2019.01.004.	Intervention/Exposure
16	Boyle SH, Mortensen L, Gronbaek M, Barefoot JC. Hostility, drinking pattern and mortality. *Addiction*. 2008. 103(1):54-9. doi:10.1111/j.1360-0443.2007.02024.x.	Publication Date
17	Breslow RA, Graubard BI. Prospective study of alcohol consumption in the United States: quantity, frequency, and cause-specific mortality. *Alcohol Clin Exp Res*. 2008. 32(3):513-21. doi:10.1111/j.1530-0277.2007.00595.x.	Outcome
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	Citation	Rationale
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	Citation	Rationale
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87	Hulsegge G, Looman M, Smit HA, Daviglus ML, van der Schouw YT, Verschuren WM. Lifestyle Changes in Young Adulthood and Middle Age and Risk of Cardiovascular Disease and All-Cause Mortality: The Doetinchem Cohort Study. *J Am Heart Assoc*. 2016. 5(1). doi:10.1161/jaha.115.002432.	Comparator
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	Citation	Rationale
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252	Taylor BJ, Shield KD, Rehm JT. Combining best evidence: a novel method to calculate the alcohol-attributable fraction and its variance for injury mortality. *BMC Public Health*. 2011. 11:265. doi:10.1186/1471-2458-11-265.	Outcome
253	Taylor J. Effects of alcohol on cardiovascular disease: originally thought to be cardioprotective, the pendulum is now swinging against alcohol, with more deaths due to drinking than lives saved. *Eur Heart J*. 2013. 34(9):627-9.	Study Design; Publication Status; Other (e.g., duplicative data, not primary research)
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258	Thygesen LC, Johansen C, Keiding N, Giovannucci E, Gronbaek M. Effects of sample attrition in a longitudinal study of the association between alcohol intake and all-cause mortality. *Addiction*. 2008. 103(7):1149-59. doi:10.1111/j.1360-0443.2008.02241.x.	Publication Date
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274	Walker S. Russia's alcohol problem. *Bmj*. 2011. 343:d5240. doi:10.1136/bmj.d5240.	Study Design
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278	White J, Greene G, Kivimaki M, Batty GD. Association between changes in lifestyle and all-cause mortality: the Health and Lifestyle Survey. *J Epidemiol Community Health*. 2018. 72(8):711-714. doi:10.1136/jech-2017-210363.	Intervention/Exposure
279	Whitfield JB, Heath AC, Madden PAF, Landers JG, Martin NG. Effects of high alcohol intake, alcohol-related symptoms and smoking on mortality. *Addiction*. 2018. 113(1):158-166. doi:10.1111/add.14008.	Comparator
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